Mediastinal Germ Cell Tumors

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8.1 Introduction

Mediastinal germ cell tumors (GCTs) have been described at least since the beginning of the twentieth century [1]. However, for many years there was some controversy whether these tumors are truly of mediastinal origin or whether they represent metastases from an occult gonadal tumor or a subtype of thymoma. Therefore, tumors with morphological features of seminoma were termed, for instance, "seminoma-like tumor" or "seminomatous thymoma" [2, 3]. In the 1970s and 1980s, the concept of primary mediastinal germ cell tumors (PMGCTs) became well established [4–7].

Although PMGCTs are histological and ultrastructural similar to their gonadal counterpart [4], the behavior of at least a subgroup of these tumors is different. For instance, in contrast to gonadal GCT, in the adult mediastinum, nonteratomatous components are regarded as malignant. In addition, PMGCTs have distinct differential diagnoses due to their location. It is important to differentiate PMGCT from these other malignancies in the mediastinum because of differences in treatment and outcome.

8.2 Demographics

PMGCTs are rare and comprise approximately 1–15 % of all mediastinal neoplasms in adults and 11 % in children [8–10]. Even though the mediastinum is the most common primary site of extragonadal GCTs in male patients, PMGCTs only account for approximately 2–5 % of all GCTs [11–13]. According to data from the Surveillance, Epidemiology, and End Results (SEER) 9 registries (1973–2007) [13], 2.1 % of all GCTs (1.8 % of seminomas, 2.4 % of nonseminomatous tumors) in white males and 4.7 % in black males are found in the mediastinum. Similarly, 2.3 % of all GCTs (2.8 % of dysgerminomas, 2.1 % of non-dysgerminomatous GCTs) in white females and 0.8 % in black females are identified in the mediastinum [13]. The incidence rates are 1.3/ 1 million for white males and 0.1/1 million for white females [13]. An epidemiologic study from Germany reported slightly lower incidence rates of mediastinal seminomas, non-seminomatous GCT in males, and non-dysgerminomas in females of 0.11, 0.2, and 0.03 per 1 million people, respectively [14].

In adults, PMGCTs occur predominantly in men; only approximately 9–14 % arise in women [13, 15–17]. The incidence of PMGCT abruptly

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increases at puberty. Overall, these tumors are more common in older adolescence and postpubertal children with a mean age of 29 years (range, 2–67 years) and peaks of incidence between ages 20 and 25 and around age 35 [13]. However, the age of the patient at the time of tumor diagnosis largely depends on the tumor type. For instance, congenital teratomas and yolk sac tumors occur predominately in very young patients, while seminomas are usually diagnosed in patients 10 years and older [18]. In contrast, sarcomatous elements are rare in PMGCT of children [19]. Similarly, mixed malignant PMGCTs are more common with increasing age. In adults, seminoma is the most common nonteratomatous component; yolk sac tumor, embryonal carcinoma, and choriocarcinoma may also occur. A rare case of placental site trophoblastic tumor presenting as a recurrence 2 years after the resection of a mediastinal teratoma in a 14-year-old male patient has also been described [20].

8.3 Clinical Features

Most mediastinal GCTs (82 % in a radiologic study) occur in the anterior mediastinum [21] and are commonly associated with the thymus [22]. In 14 %, multiple mediastinal compartments are affected [21]. Because of the relative large space in the anterior mediastinum, mediastinal GCTs, especially slow growing mature teratomas or seminomas, are often incidental findings [15, 23, 24]. The clinical presentation of patients with mediastinal GCT depends largely on tumor size. Symptoms such as cough, chest pain, hemoptysis, dyspnea, postobstructive pneumonia, and/or superior vena cava (SVC) syndrome occur in general due to compression of adjacent organs including large airways, great vessels, the heart, and phrenic nerve [25–28]. SVC syndrome, for instance, was described in approximately 10–25 % of anterior mediastinal seminomas [7, 15, 29–31]. Rarely, the tumor can erode into an adjacent bronchus which, in case of a mature teratoma, can lead to expectoration of hair (trichoptysis) or sebaceous debris [32]. Other rare complications include erosion into the pericardium, adjacent vascular structures, or through the skin to form a draining fistula [33, 34]. Painful gynecomastia was described in a patient with seminoma [35]. This patient had high circulating estradiol and beta-HCG levels that normalized after resection of the tumor.

Klinefelter syndrome is the only risk factor that has been identified for PMGCTs. This syndrome was identified in 8–22 % of male patients with PMGCT [27, 28, 36]. A study of 696 men with Klinefelter syndrome of the Danish Cytogenetic Register revealed a 67 times higher risk to develop PMGCT for patients with the syndrome than male patients without it [37]. Patients with PMGCT associated with Klinefelter syndrome are in general younger 4.5–31 years old than patients without the syndrome [27, 28, 37, 38]. In a study by Nichols, patients with Klinefelter syndrome and PMGCT had a median age of 15 years (range, 14–28 years) in contrast to 28 years (range, 18–35 years) in patients with PMGCT without the syndrome [27]. In some patients the diagnosis of Klinefelter syndrome is only established after a PMGCT has been identified. Therefore, a cytogenetic analysis has been recommended for young male patients with PMGCT [39]. The association of Klinefelter syndrome with PMGCTs is thought to be related to a persistent elevation of gonadotropin levels in these patients [37]. Gonadotropins might contribute to the malignant transformation of incompletely migrated primordial cells/germ cells [37]. However, genetic factors on the X chromosome have also been hypothesized [40]. Interestingly, the association with Klinefelter syndrome appears to be specific to PMGCT and pineal GCT but not gonadal or retroperitoneal GCT [38]. Furthermore, Klinefelter syndrome appears to be only associated with non-seminomatous PMGCT including teratoma with seminomatous or embryonal carcinoma and yolk sac tumor, pure teratoma, and yolk sac tumor. The reason for this restricted association of Klinefelter syndrome with non-seminomatous GCT of the mediastinum and pineal gland is not entirely clear. In

addition a small subgroup of prepubertal children with PMGCT and Klinefelter syndrome present with precocious puberty due to HCG-producing PMGCT [40].

PMGCTs most commonly metastasize to the lung and bone, but metastases are also found in the liver, spleen, brain, tonsils, and subcutaneous tissue [6]. Only a minority of patients with mediastinal GCT has metachronous testicular tumors. Bokemeyer et al. [41] noted metachronous testicular tumors in only 1.1 % of men with mediastinal GCT. Fossa et al. [42] reported that three (of 15, 20 %) men with mediastinal GCT presented with testicular germ cell neoplasia in situ.

8.4 Imaging Findings

Teratomas usually present as an anterior mediastinal mass on chest X-ray. Calcifications are seen in 25 % of cases [21, 33]; well-formed teeth or bone are very suggestive of the diagnosis. Occasionally, areas of radiolucency suggest fat. Diffuse mediastinal widening or a mediastinal mass partially obscured by pulmonary parenchymal consolidation or cardiomegaly has also been described [21]. CT and MRI better characterize densities within the lesion suggestive of fat, sebaceous material, or cystic elements [21]. A multilocular cystic anterior mediastinal mass with fat content on CT scan is virtually diagnostic of mature teratoma. However, mature teratomas can also present as more heterogeneous masses, containing soft tissue, fluid, fat, and calcium attenuation. On CT scans, the majority of mature teratomas have well-defined margins against the adjacent lung parenchyma with a lobulated contour present in about half of the cases. The most common MR imaging finding is also a heterogeneous mass with signal intensities isointense with muscle, fluid, and fat [21]. Effusions are rather uncommon [21].

Immature teratoma can present as a large unilateral mass with heterogeneous densities and displacing mediastinal structures [43]. Malignant elements may exhibit an irregular thick wall with indistinct margins, obliteration of tissue planes, invasion of mediastinal structures, and/or extensive necrosis [44–46].

Seminomas typically appear as large and bulky, well-marginated, lobulated masses on chest X-ray [29, 47]. While its margins are usually well defined, invasion of the adjacent lung may result in irregular borders. On CT scan, seminomas appear large and coarsely lobulated with a homogeneous attenuation equal to that of soft tissue that may obliterate tissue planes or directly invade adjacent structures [47]. Seminomas show slight contrast enhancement [47]. Areas of low attenuation may also be detected [48]. Ringlike and stippled calcifications within a mediastinal seminoma are uncommon [49]. Rarely, when central necrosis occurs with little residual solid tumor (8 %), the lesion may exhibit extensive unilocular or multilocular low attenuation areas and may mimic cystic anterior mediastinal lesions [50–52]. Metastatic intrathoracic lymphadenopathy may also be observed [53].

Non-seminomatous GCTs manifest as large bulky anterior mediastinal masses that frequently exert mass effect on adjacent thoracic structures. Tumor margins may be well circumscribed or poorly defined [48]. CT typically demonstrates large heterogeneous masses with extensive central areas of low attenuation due to necrosis and hemorrhage. Residual viable tumor in general presents as lobular papillary soft tissue components in the periphery of the lesion that usually enhance [47]. Adjacent mediastinal tissue planes are frequently obliterated, and there may be radiologic findings of mediastinal, lung, or chest wall invasion. Associated pleural and pericardial effusions are common [54]. Metastases to regional lymph nodes may present as mediastinal lymphadenopathy [55, 56].

8.5 Histogenesis

Several hypotheses for the histogenesis of PMGCTs have been proposed:

(i) Primordial germ cells fail to complete the normal migration along the urogenital ridge

to the gonadal ridges during embryonal development. This may be due to an abnormality in the primordial germ cell itself or in its microenvironment [57]. Different stages of development of the primordial cells and microenvironmental conditions may determine the final histology of the tumors at these sites [58].

(ii) Germ cells transformed in the testes undergo reverse migration [59, 60]. This hypothesis was supported by the lack of significant differences of chromosome aberrations between gonadal and mediastinal GCTs. For instance, nonrandom chromosomal changes were found to be essentially the same in gonadal and mediastinal GCT, and the incidence of isochromosome 12p was similar between gonadal and mediastinal GCT [59]. However, there are some biological differences between mediastinal nonseminomatous GCTs compared to its gonadal or retroperitoneal counterparts including worse prognosis and higher incidence of yolk sac tumor elements and leukemia in patients with mediastinal GCTs. Although these differences might result from differences in the cell of origin which would dispute this hypothesis, they also could result from the tumor's microenvironment.

(iii) Since mediastinal GCTs are usually associated with the thymus, mediastinal GCT might arise from thymic cells with germ cell potential.

Although morphologically similar, evidence suggests histogenetic differences between primary mediastinal and testicular GCTs [61–63]. For instance, the ploidy of mediastinal tumors is closer to those of testicular GCT of children that are usually diploid [61]; in contrast, testicular GCTs of adults are consistently aneuploidy [58]. A study comparing k-ras-2 gene sequences between mediastinal and testicular seminomas showed that 8 % (1 of 13) of mediastinal seminomas had a k-ras mutation in codon 13, while 15 % (2 of 13) of testicular seminomas had k-ras mutations in codon 12 [62]. Other studies confirmed that k-ras mutations in testicular GCT, if identified, are in codon 12 [64, 65]. Furthermore, weak p53 immunostaining was identified in 31 % of mediastinal seminomas in contrast to 77–90 % of testicular seminomas and 94 % of testicular nonseminomatous GCT [66]. A unique kit gene mutation on exon 17 was identified in about 50 % of primary mediastinal seminomas [63].

8.6 Histologic Classification of Mediastinal Germ Cell Tumors

PMGCTs are classified according to the WHO [67], identical to the classification of gonadal GCTs. PMGCTs are divided into seminomatous tumors (pure), non-seminomatous tumors (yolk sac tumor, embryonal carcinoma, choriocarcinoma, and mixed GCTs), and teratomas. Slightly more (52–60 %) PMGCTs are of nonseminomatous than seminomatous type [13, 68].

While the majority of PMGCT only has one tumor component, a study showed that 34 % of tumors had multiple components, and therefore adequate sampling of the tumor is essential [15]. The most common component of these malignant PMGCTs was a seminoma (88 % of cases), but embryonal carcinomas, malignant teratomas, choriocarcinomas, and yolk sac tumors were also identified.

8.6.1 Teratoma

Teratomas are the most common MGCT accounting for 43–75 % of mediastinal GCTs (Table 8.1) [68, 69]. They usually occur in the anterior medi-

Table 8.1 Frequency of mediastinal germ cell tumors [68, 69]

Mediastinal germ cell tumor	Frequency (% cases)
Teratoma	43–75
Seminoma	10–37
Yolk sac tumor	2–12
Embryonal carcinoma	2–8
Choriocarcinoma	2

astinum but occasionally can be seen in the posterior mediastinum [33, 68, 70]. Mediastinal teratomatous tumors include mature (63 %) and immature teratomas (4 %) and teratomas with other malignant components (i.e., sarcoma, other malignant germ cell elements, or carcinoma) (33 %) [68].

Mature mediastinal teratomas have been described in patients between 1 month and 73-year-olds with a peak incidence in early adulthood (mean 28 years) [33]. On gross examination [33] benign teratomas are usually encapsulated and well circumscribed (Fig. 8.1). The average tumor size is 10.5 cm (range, 2.5–27 cm). Similar to mature teratomas in other locations, cysts might occur within the tumor (Fig. 8.1) [70]. However, in contrast to their gonadal counterpart, monodermal teratomas such as struma ovarii have not been described in the mediastinum.

In contrast to adult gonadal teratomas or congenital/pediatric teratomas, in the adult mediastinum, the distinction between mature and immature teratoma is critical to patient management because immature teratomas have in general a worse prognosis.

At present, there is no grading scheme for extragonadal immature teratomas; however, it has been suggested to report the percentage of immature elements. Teratomas with other malignant germ cell elements (e.g., seminoma, embryonal carcinoma, yolk sac tumor) are regarded as malignant non-seminomatous GCT. Other adverse histologic features include sarcomatous or carcinomatous transformation, or an associated hematologic malignancy (see Chapter 12).

8.6.2 Seminoma

Pure seminomas represent the second most common mediastinal GCT accounting for approximately 10–37 % of all mediastinal GCTs (Table 8.1) [68, 69]. They usually occur in the anterior mediastinum [23, 51]. The vast majority of mediastinal seminomas are identified in men; only rare cases have been reported in women [6, 26, 29, 69, 71, 72]. The reported age ranges between 11 and 79 years with a mean age of 46.5 years in one study [51]; other studies report that the tumor most commonly occurs in the third decade followed by the fourth and second decade [6].

Seminomas vary in size from a few centimeters to over 16 cm in greatest diameter [23]. On gross examination, mediastinal seminomas are usually soft and have a smooth and glistening outer surface or may show a lobulated appearance; the cut surface is coarsely lobular or exhibits a discrete nodular pattern, and the color varies from white to light tan. In some cases, solid areas may alternate with large cystic spaces containing necrotic material, whereas in other areas the tumor may have the appearance of an entirely cystic mass.

Some microscopic features appear to be unique to mediastinal seminomas (Table 8.2) (Fig. 8.2). They frequently involve the thymus, showing cyst formation and thymic epithelial cell hyperplasia [50, 73]. Cystic seminomas may histologically mimic multilocular thymic cysts [50]. These tumors characteristically show areas of lymphoid hyperplasia (Fig. 8.3), cysts lined by squamous epithelium, and cholesterol cleft granulomas. The seminomatous component might be growing along the cystic walls of the tumor making its distinction from thymic follicular hyperplasia or thymoma (Fig. 8.4) difficult. Therefore, a high level of suspicion is necessary in the case of cystic lesions of the thymus, especially if associated with a granulomatous response; extensive sampling of these cystic tumors is critical. Seminomas might be especially difficult to identify in small biopsies from the mediastinum because of cystic changes, and inflammatory and granulomatous response may obscure the diagnostic tumor cells.

In mediastinal seminomas the neoplastic cells can sometimes be arranged in cell nests that are separated by thin fibrovascular septa. The fibrovascular septa will characteristically be infiltrated by a large number of lymphocytes. Foci with giant cells of the syncytiotrophoblast type have been observed in <5 % of mediastinal GCTs [23]. A few cases of anaplastic seminoma have also been reported in the anterior mediastinum [74]. Rarely, in the mediastinum, seminomas can be

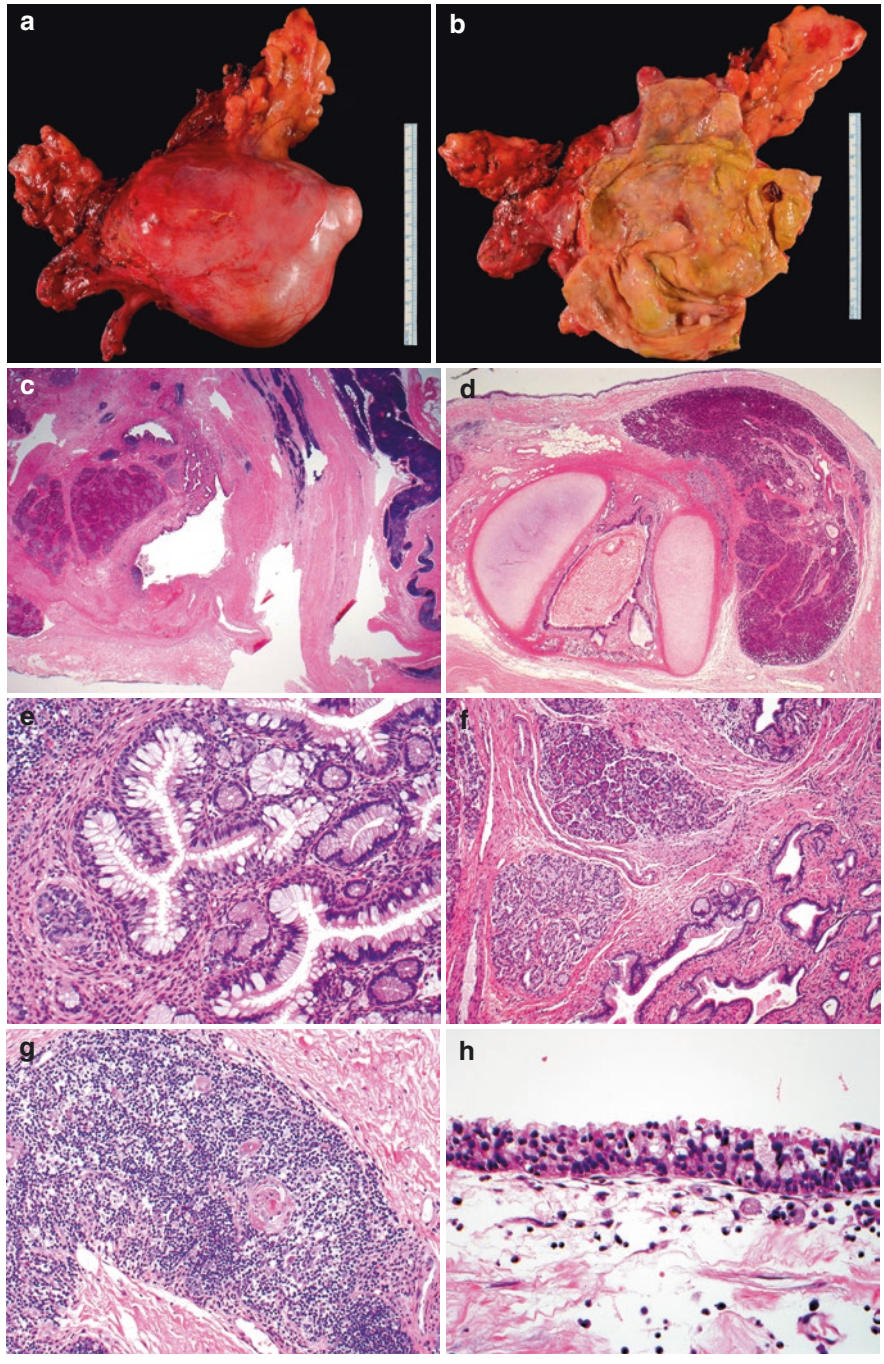

Fig. 8.1 Mature cystic teratoma. (**a**) A well-circumscribed mass with smooth borders has focal yellow tissue at the rim. (**b**) Sectioning reveals a cyst with largely smooth lining and focal small nodular areas. (**c**) On microscopy, the cyst wall is comprised of fibrous tissue with glandular and cystic areas and thymic parenchyma (*upper right*). (**d**) Multiple germ layers are present including the mesoderm (cartilage, adipose tissue) and endoderm (respiratory epithelium (**e**, **f**) and pancreatic tissue (**f**)). This teratoma is in a background of thymic parenchyma (**g**). The cyst is lined by benign ciliated respiratory epithelium (**g**). Magnification × 12.5 (**c**), 20 (**d**), 200 (**e**, **g**), 100 (**f**), 400 (**h**)

Table 8.2 Histopathologic features of primary mediastinal seminomas (Figs. 8.2 and 8.3) [51, 73]

Histopathologic features	Frequency (% cases)
Lymphocytic infiltration	100
Fibrous septa/stroma	91
Prominent tumor cell nucleoli	91
Clear tumor cell cytoplasm	87
Distinct tumor cell borders	87
Non-necrotizing granulomatous inflammation	46–74
Cellular pleomorphism	43
Necrosis	35
Thymic remnants	27
Prominent cystic changes	8
Intercellular edema	4
Syncytiotrophoblasts	4
Mean mitotic count/ten high-power fields	4.4 (range, 0–16)

associated with another non-GCT such as primary leiomyosarcoma [75].

Most seminomas (96 %) of the mediastinum harbor chromosome 12p abnormalities, including 12p amplification (87 %) or isochromosome 12p (65 %) [73].

8.6.3 Other Non-seminomatous Mediastinal Germ Cell Tumors

Other non-seminomatous mediastinal GCTs are rare (Table 8.1).

The histopathologic characteristics of non-seminomatous mediastinal GCTs such as embryonal carcinoma, mixed germ cell tumors, yolk sac tumors (Fig. 8.5), and choriocarcinomas are similar to their gonadal counterparts and are described elsewhere in this book.

8.6.4 Sarcomatoid Component of Mediastinal Germ Cell Tumors

Sarcomatous differentiation of GCT is most frequently seen in the mediastinum and may occur in association with mature teratomas or, less commonly, with other malignant GCTs including immature teratoma, choriocarcinoma, yolk sac tumor, and seminoma [76]. The most common type of heterologous differentiation is rhabdomyosarcoma; other sarcomatous components include angiosarcoma, leiomyosarcoma, glioblastoma multiforme, malignant peripheral nerve sheath tumor, epithelioid hemangioendothelioma, and undifferentiated sarcoma (Fig. 8.6) [76]. Cases with components of chondrosarcoma, osteosarcoma, liposarcoma, malignant fibrous histiocytoma, primitive neuroectodermal tumor, and neuroblastoma have also been reported. Any somatic-type malignancy should be reported because PMGCTs with sarcomatous differentiation are unresponsive to conventional GCT therapy and their prognosis is dismal [76]. An estimate of the involved area may also be helpful (see also Chapter 12).

Because of the poor prognosis of patients with PMGCT with sarcomatous component, its distinction from immature mesenchyme in an immature teratoma is critical. In general, the spindled component of immature teratoma is cytologically bland, is relatively monomorphic, and is typically condensed around teratomatous glands with a concentric, swirling growth pattern. In contrast, sarcomatous differentiation is characterized by an expansile and architectural complex (i.e., intersecting fascicles or storiform pattern) growth with infiltration of the surrounding tissues; usually has a greater degree of nuclear pleomorphism and hyperchromasia, obvious mitotic activity, and obvious malignant heterologous differentiation; and lacks intimately admixed glands. Rhabdomyoblasts can be distinguished from hepatoid yolk sac tumor or other eosinophilic mimickers by the demonstration of expression of smooth muscle markers including desmin and myogenin. In contrast to stromal overgrowth, sarcomatous differentiation shows independent growth by virtue of replacing teratomatous glands or other germ cell elements, thus forming an area of pure sarcoma [77].

Patients with PMGCT with sarcomatous component appear to have a worse prognosis than their gonadal counterparts. Malagon et al. [76] showed that only 18 % of patients with PMGCT

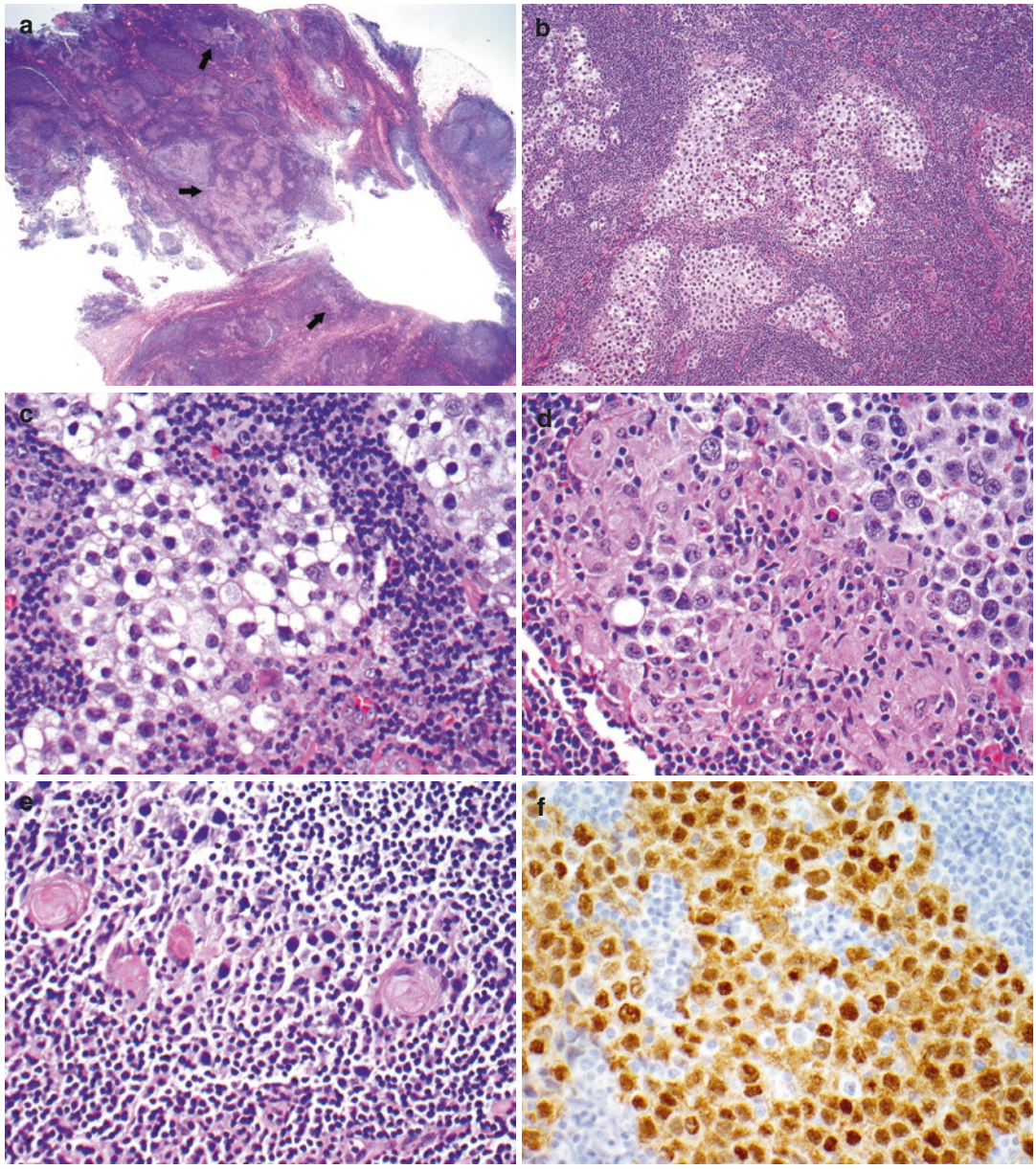

Fig. 8.2 Seminoma arising in the thymus. (**a**) Lymphoid tissue with germinal centers contains scattered nests of atypical cells (*arrows*). (**b**) These irregular nests are comprised of cohesive atypical epithelioid cells, many of which have clear cytoplasm (**c**) and others have more eosinophilic cytoplasm (**d**). Many tumor cells have prominent nucleoli. Occasional Hassall corpuscles within the lymphoid tissue suggest a background of thymic parenchyma (**e**). The neoplastic cells are positive for OCT4 (**f**) and CD117 (**g**) and are negative for CD30 (**h**) and keratin AE1/AE3 (**i**). Magnification × 12.5 (**a**), 100 (**b**), 400 (**c**–**i**)

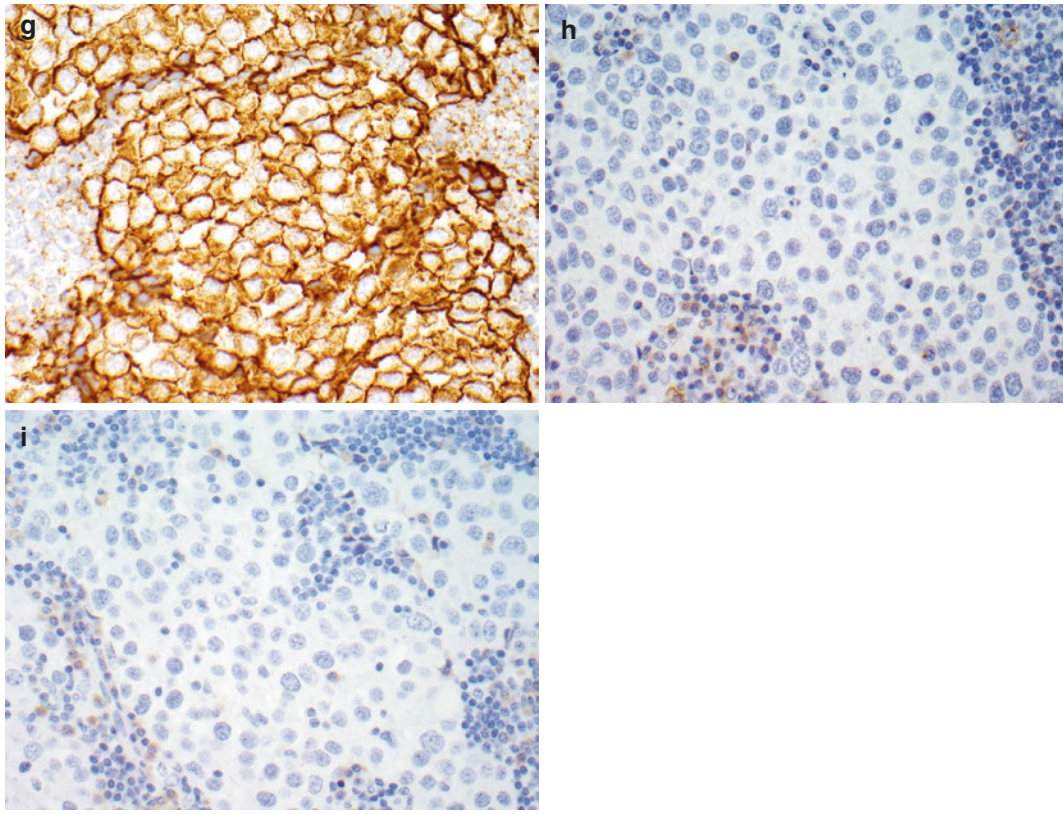

Fig. 8.2 (continued)

with sarcomatous component were alive at 12–42 months, while 82 % had died from disease between 1 and 37 months. Patients with mediastinal tumors usually die due to local compromise of vital structures. In contrast 56 % of patients with testicular GCT with sarcomatous component were alive at 1–72 months, and only 44 % had died from disease between 5 and 96 months. Despite their better prognosis, testicular GCTs with sarcomatous component have a greater tendency for metastases (75 %) compared to mediastinal tumors (18 %). These differences in tumor behavior and prognosis may be due to location and size of the lesion and their resectability. In the study by Malagon et al. [76], the majority of extragonadal tumors were larger and bulkier than the gonadal lesions and were more commonly excised with positive margins. Moreover, the mediastinal location allows tumors to grow much larger before becoming symptomatic, so increasing the potential for malignant transformation. Because of the large size, the majority of PMGCTs were extensively infiltrative at the time of surgery making complete resection very difficult.

8.7 Ancillary Studies

Ancillary studies might be utilized to distinguish PMGCT from other primary or secondary mediastinal tumors. Immunohistochemical and cytogenetic studies are most helpful.

8.7.1 Immunohistochemical Studies (Table 8.3)

In general, the immunophenotype of PMGCT is similar to its gonadal counter. However, there are

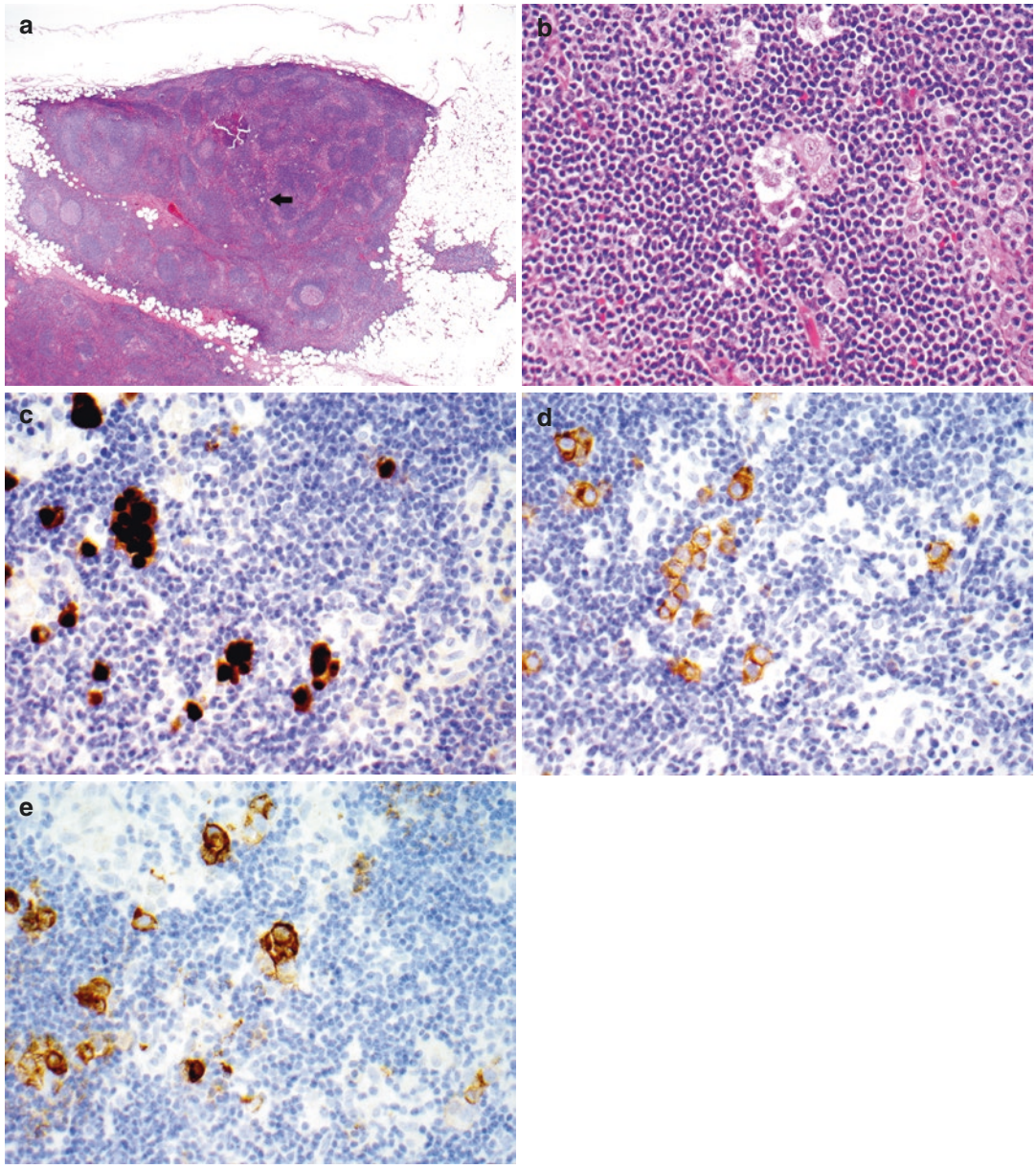

Fig. 8.3 Seminoma. (**a**) In this case there are only occasional single tumor cells or small clusters of tumor cells in a lymphoid background with prominent lymphoid hyperplasia. On low magnification these tumor cells are difficult to identify and might be easily missed (*arrow*). (**b**) On higher magnification small nests of tumor cells are identified. These tumor cells have clear cytoplasm and some have prominent nucleoli. The neoplastic cells are highlighted by OCT3/4 (**c**), CD117 (**d**), and PLAP (**e**). Magnification × 20 (**a**), × 400 (**b**–**e**)

some significant differences in the expression of some antigens, especially on tumor cells of seminomas [78]. For instance, in a study by Suster et al. [78], the low molecular weight keratin CAM 5.2, which shows a strong dot-like paranuclear staining pattern in seminomas, is expressed in 80 % of mediastinal seminomas but only in 20 % of testicular seminomas. Similarly, PLAP is expressed in 92.5 % of mediastinal seminomas (Fig. 8.3) but only in 50 % of testicular seminomas.

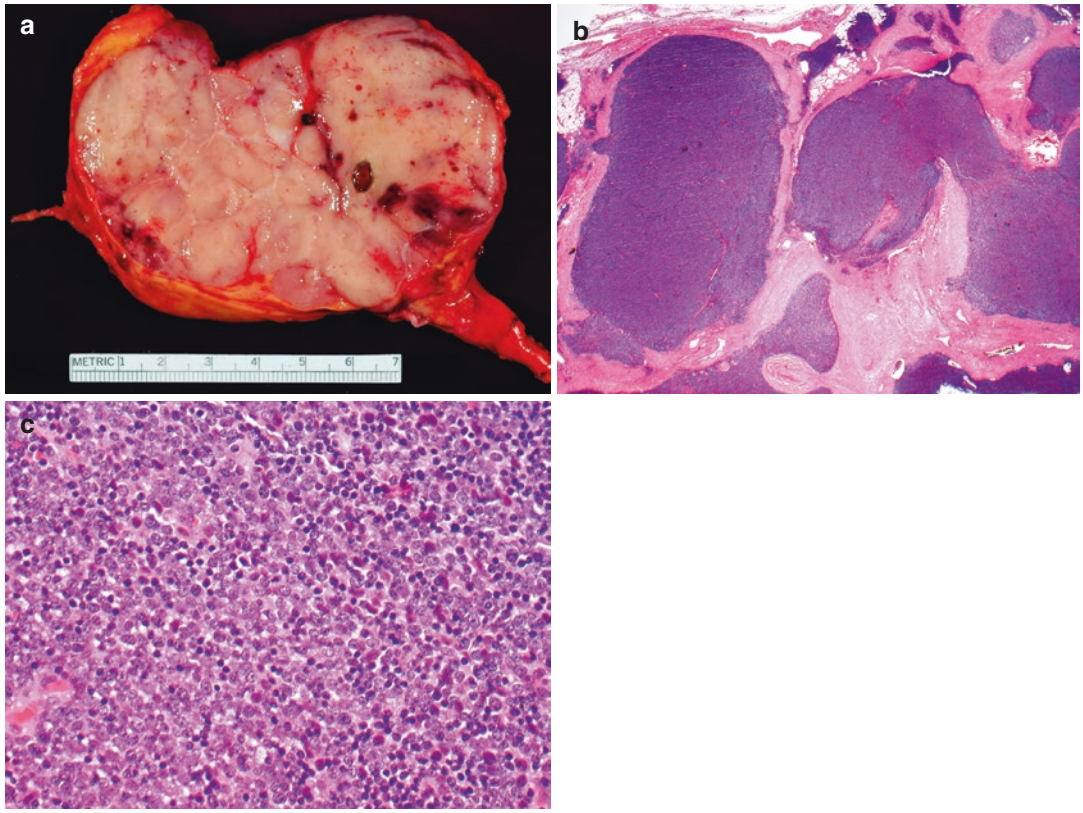

Fig. 8.4 Thymoma, WHO type B2. (**a**) On gross examination, there is a well-circumscribed, tan, lobulated tumor with intervening fibrous septa. (**b**) The lobulated architecture is also apparent on low-power microscopy that reveals hypercellular lobules that are separated by fibrous septa. (**c**) On high magnification there is a mixture of larger epithelial tumor cells and small lymphocytes. Magnification × 12.5 (**b**), × 400 (**c**)

OCT4 has a high sensitivity and specificity for seminoma and embryonal carcinoma [79–81]. Nearly 100 % of seminomas and embryonal carcinomas show nuclear reactivity with OCT4, and the specificity seems superior to other available markers (Fig. 8.2f) [79–81].

Keratins can be expressed in 39–80 % of mediastinal seminomas and therefore might present a pitfall mimicking carcinoma [51, 77, 78]. However, in most cases, the epithelial markers highlight only a small proportion of tumor cells with variable intensities [73].

Strong membranous CD117 (kit) immunoreactivity has been reported in 75–100 % of seminomas (Figs. 8.2g and 8.3d) [82]. However, in the mediastinum, CD117 is not specific to seminomas because it is also expressed in other non-germ cell tumors including small cell carcinoma and adenocarcinomas of the lung [83] and thymic carcinomas [84, 85]. In addition, embryonal carcinoma, yolk sac tumor, and choriocarcinoma may show some degree of weak CD117 reactivity (Fig. 8.5e).

CD30 is expressed in over 80 % of embryonal carcinomas. However, CD30 is also expressed in various hematopoietic malignancies which commonly occur in the mediastinum such as mediastinal large B-cell lymphoma or Hodgkin lymphoma (Fig. 8.7) [86] but also occasionally in yolk sac tumors and rarely seminoma [78].

AFP is not a reliable marker for yolk sac tumors because of its low sensitivity [87]. Furthermore, AFP can be expressed in 60 % of hepatoid adenocarcinomas of the lung [88]. Serum evaluation of AFP and [beta]-human chorionic gonadotropin (beta-HCG) is frequently

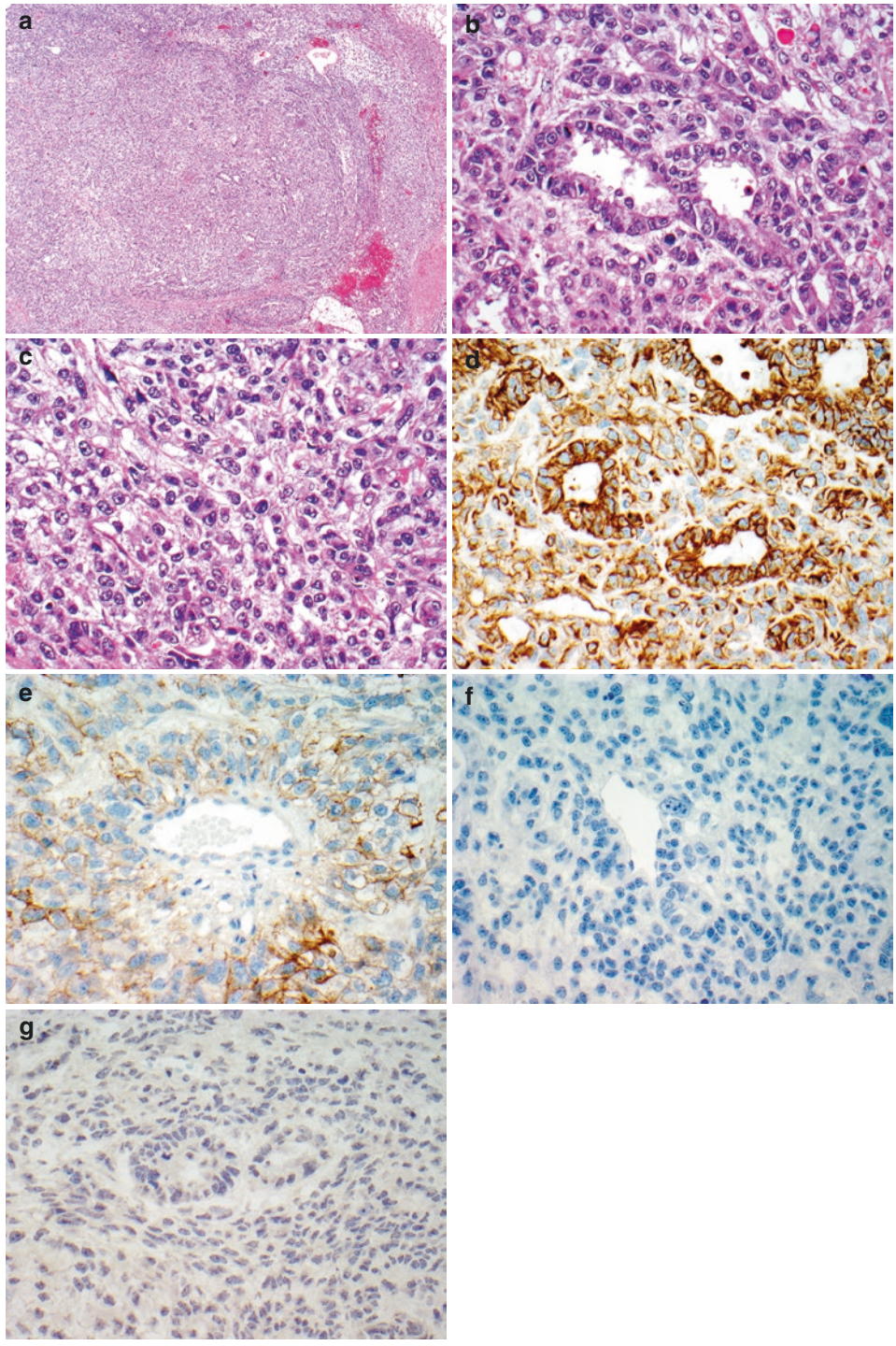

Fig. 8.5 Yolk sac tumor. (**a**) This tumor shows a predominant solid growth pattern with a few glandular structures. (**b**) Schiller-Duval bodies are identified. (**c**) The neoplastic cells are round to oval with clear to eosinophilic cytoplasm, open chromatin, and prominent nucleoli. The tumor cells express keratin AE1/AE3 (**d**), some express weakly CD117 (**e**), and they are negative for PLAP (**f**) and OCT4 (**g**). Magnification × 40 (**a**), × 400 (**b**–**g**)

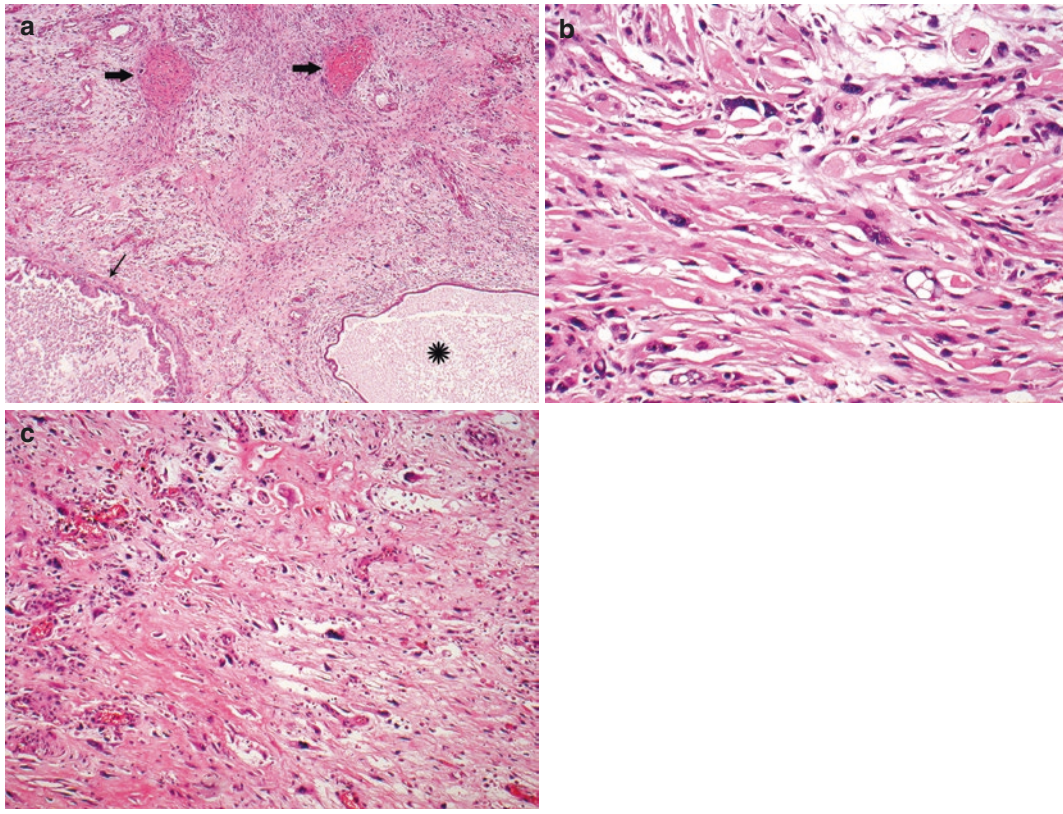

Fig. 8.6 Spindle cell sarcoma arising in teratoma. (**a**) Low magnification view reveals a neoplastic spindle cell proliferation with focal osteoid (*thick arrow*). A cyst lined by glandular epithelium (*thin arrow*) and another cyst lined by bland cuboidal epithelium (*star*) are suggestive of a teratoma. (**b**, **c**) High-power view shows pleomorphic spindle cells with dark nuclear chromatin consistent with a spindle cell sarcoma. Magnification × 40, (**a**), × 400 (**b**, **c**)

more sensitive than immunohistochemistry. However, beta-HCG is also not entirely specific to GCT and can be seen in 10–60 % of adenocarcinomas of the lung [89, 90].

Although placental-like alkaline phosphatase (PLAP) has traditionally been the marker of choice for GCTs (mostly seminoma), in the setting of an "undifferentiated" neoplasm in the mediastinum, its lack of sensitivity, generally high background staining, and the development of newer antibodies have rendered this stain less useful in current diagnostic practice.

8.7.2 Cytogenetic Studies

Bosl et al. [11] found that the isochromosome of chromosome 12 [i(12p)] as evaluated by FISH studies is a useful marker for GCT in males. This was further confirmed in a study by Sung et al. [73] that showed abnormalities of chromosome 12p including 12p amplification and i(12p) in 22 out of 23 cases of mediastinal seminoma. Chaganti et al. [59] performed karyotypic analysis of 13 PMGCT and observed characteristic i(12p) in 69 % cases (9/13).

Table 8.3 Immunophenotype of mediastinal germ cell tumors and their mimickers [Frequency (% positive cases)]

Immunostain	Seminoma	Embryonal carcinoma	Yolk sac tumor	Teratoma	Choriocarcinoma	Lung adenocarcinoma	Small cell carcinoma	Thymic carcinoma	Malignant mesothelioma	NUT midline carcinoma
OCT 4 [73, 115, 150–152]	100	100	0	0	0	N/A[a]	N/A	0	0	0
OCT 3/4 [153–157]	100	82–100	38	0	0	0	N/A	N/A	N/A	0
CD117 [73, 82–85, 150, 157–161]	75–100	77–100	30–59	43	0	17	82	80–86	5	0–25
SALL4 [150, 157]	100	97	100	29	0	N/A	N/A	0	N/A	0
AFP [78, 88, 89, 141, 150, 157, 158]	0	0	56–100	N/A	0	60[b]	N/A	N/A	N/A	0
Beta-HCG [78, 89, 90, 141, 157, 162]	3	33	0	10–60	100	7–60	0	0	0	0
PLAP [73, 78, 141, 150, 157, 163–165]	43–100	59	40	0	0	25–67	N/A	0	15	0
D2–40 [153, 158, 166]	96–100	35	3	N/A	N/A	7	N/A	N/A	96	N/A
CAM 5.2 [73, 78, 157, 161, 165, 167–169]	48–80	100	100	100	100	100	100	100[c]	100	73
Keratin AE1/AE3 [73, 78, 157, 158, 167, 168, 170]	0–43	100	100	100	100	100	50–100	100	100	31
High molecular weight keratin [73, 168, 171–173]	0–39	0	N/A	N/A	N/A	25–82	0	100[d]	89[e]	N/A
CK7 [73, 103, 157, 161, 164, 171, 174, 175]	39–41	100	N/A	97	N/A	79–100	43	80	65–81	40
CK20 [73, 103, 157, 174]	0	0	0	0–100	N/A	10	0	N/A	0	0
EMA [73, 153, 157, 165, 167, 171, 176–178]	2–9	33	29	100[f]	54	95–100	N/A	100	96[e]–98	71

CD5 [84, 157, 165, 175, 179, 180]	0	N/A	N/A	N/A	N/A	10	0	20–70	0–12	33
CD30 [73, 78, 82, 150, 153, 157, 165, 181]	0–2	73–100	0–11	40[g]	0	0	0	N/A	0	12
TTF-1 [103, 157, 161–163, 165, 172, 177, 179, 182–184]	0	0	0	50	N/A	57–89	85–95	0	0	33
Calretinin [167, 173, 177, 185, 186]	9	0	N/A	0	0	4–10	41	N/A	87–100	N/A
WT-1 [157, 179, 182]	N/A	N/A	0	N/A	N/A	0	N/A	5	58–93	0
NUT [157, 187, 188]	19–71%[h]	0	5	N/A	N/A	N/A	N/A	6[i]	N/A	100

[a]N/A, not available
[b]60% of hepatoid lung adenocarcinoma
[c]Thymic carcinoma with clear cell features
[d]Spindle cell thymic carcinoma
[e]Epithelioid malignant mesothelioma
[f]EMA is expressed in all non-neural components of mature teratoma
[g]Presence of CD30 confined to respiratory component, squamous component, GI epithelium, nerve, or cartilage [153], negative in immature teratoma
[h]71% in spermatocytic seminoma, 19 % in conventional seminoma
[i]Tumors in thymic region

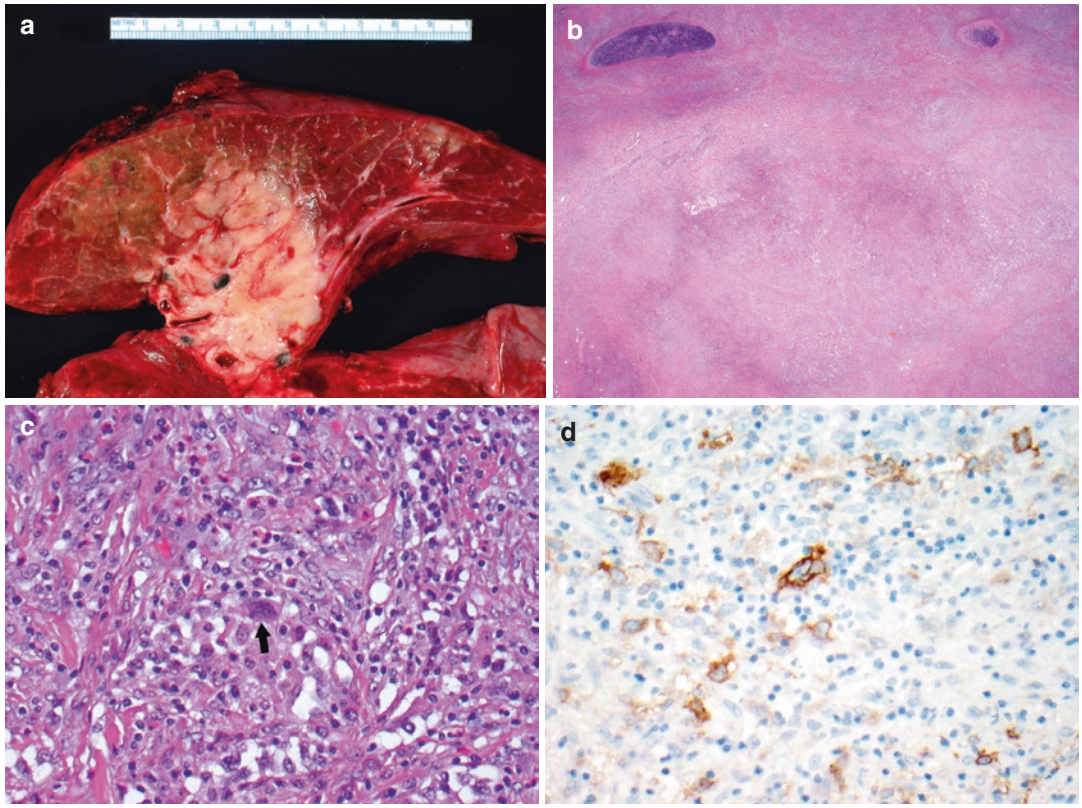

Fig. 8.7 Classical Hodgkin lymphoma, nodular sclerosing type. (**a**) A pneumonectomy specimen contains a 6.0 cm left centrally located, ill-defined, lobulated, yellow-white lung mass. (**b**) On low-power microscopy, there is a fibrotic, vaguely lobulated mass in a central location (note residual hyaline cartilage of a large airway in the upper left and right corners). (**c**). On high power, scattered large, multinucleated Reed-Sternberg cells (*arrow*) are apparent in a background of a mixed inflammatory background predominantly comprised of lymphocytes, eosinophils, macrophages, and plasma cells. The large atypical cells mark with CD30 (**d**). Magnification, × 12.5 (**b**), × 400 (**c**, **d**)

8.8 Differential Diagnosis of Mediastinal Germ Cell Tumors (Tables 8.4 and 8.5)

8.8.1 Germ Cell Tumors Metastatic to the Mediastinum

Although rare, testicular GCT can metastasize to the mediastinum [91]. However, in most mediastinal GCTs, examination of the testes fails to reveal a primary tumor. For instance, in 16 patients with extragonadal GCTs, the testicles did not have any palpable lesion [92]. However, occult testicular tumors were later identified in 10 of 12 patients with retroperitoneal GCT but in none of the mediastinal GCT. Therefore, not all testicular GCTs can be identified by palpation alone. In a study of 20 autopsy cases of mediastinal GCT, Luna and Valenzuela-Tamaris [93] identified only two cases in which the testes contained either an occult tumor or a well-defined testicular scar. Moreover, of 78 autopsies of patients with testicular GCTs, no autopsy showed solely metastases in the anterior mediastinum without involvement of other mediastinal lymph nodes (middle/posterior) [94]. In another such study of 220 cases of metastasizing testicular tumors, no metastases were documented in the mediastinum [95]. These studies emphasize that testicular GCT can metastasize to the mediastinum, but that appears to be rather exceptional, and GCTs in the mediastinum are usually

Table 8.4 Features that might facilitate the distinction between mediastinal germ cell tumors and their mimickers

Diagnosis	Distinguishing feature(s)
Seminoma	Lymphocytic infiltrate
	Cyst formation possible
	Intense staining for OCT4
	Isochromosome 12p abnormalities by FISH
Thymoma	Lobulated architecture
	OCT4 negative
Thymic carcinoma	OCT4 negative
NUT carcinoma	NUT immunostain shows a speckeled nuclear staining pattern
	t(15;19) by FISH, RT-PCR
Metastatic carcinoma	Morphologic features
	Immunophenotype
Synovial sarcoma	t(X;18), FISH, RT-PCR
Lymphoma	Immunophenotype
	Flow cytometry
	B-cell or T-cell receptor rearrangement studies

of primary origin. However, the possibility of mediastinal GCT of testicular origin exists and must be excluded. A careful review of the past medical history, physical examination, and imaging studies are necessary to distinguish between primary and metastatic disease. Moreover, retroperitoneal tumor metastases are virtually always present in cases of testicular seminoma that have metastasized to the mediastinum.

8.8.2 Thymic Cysts

Thymic cysts may be unilocular or multilocular and can potentially mimic teratoma or seminoma. The unilocular cysts, remnants of the third branchial pouch-derived thymopharyngeal duct, may be lined by cuboidal, columnar, or sometimes squamous epithelium and contain thymic tissue within the cyst wall (Fig. 8.8)

Table 8.5 Differential diagnosis of tumors that might occur in the mediastinum by morphologic pattern

Morphologic pattern				
Epithelial-lined cyst	Mixed epithelial and spindled	Poorly differentiated	Papillary	Clear cells
Mature teratoma	Immature teratoma	Embryonal carcinoma	Embryonal carcinoma	Seminoma
Seminoma	Yolk sac tumor	Seminoma	Yolk sac tumor	Yolk sac tumor
Thymic cyst	Malignant mesothelioma	Malignant mesothelioma	Malignant mesothelioma	Thymic clear cell carcinoma
Enteric cyst	Sarcomatoid carcinoma	Thymic carcinoma	Myxopapillary ependymoma	Metastatic Muellerian clear cell carcinoma
Bronchogenic cyst	Synovial sarcoma	Lymphoma		Metastatic renal cell carcinoma
Epidermal inclusion cyst	Pleuropulmonary blastoma	NUT carcinoma, t(15;19)		
Dermoid cyst	Congenital peribronchial myofibroblastic tumor	Epithelioid angiosarcoma		
Branchial cleft cyst	Pulmonary hamartoma	Lung adenocarcinoma		
Thyroglossal duct cyst	Thymoma (WHO type AB)	Melanoma		
Epidermoid cyst	Spindle cell epithelial tumor with thymus-like differentiation (SETTLE)	Carcinoma showing thymus-like differentiation (CASTLE)		
	Metastatic Wilms' tumor			

Modified from [77]

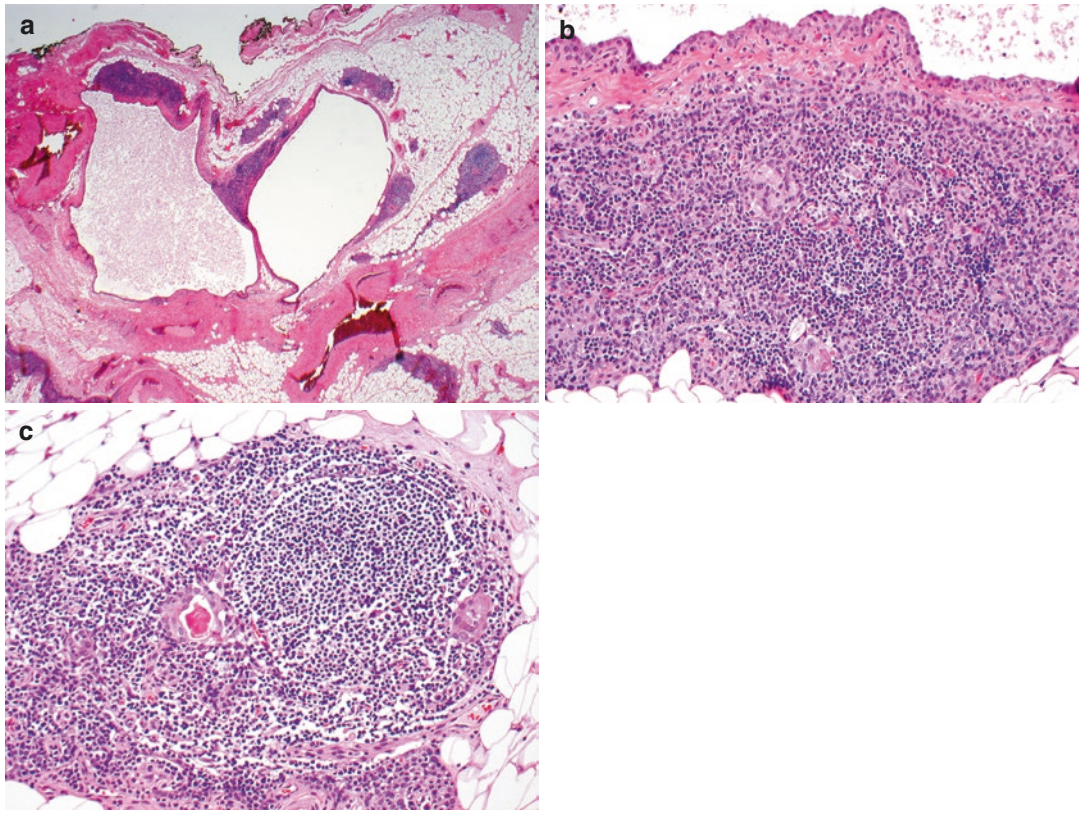

Fig. 8.8 Thymic cyst. (**a**) Cystic structures are surrounded by a lymphoid and adipose tissue. (**b**) The cysts are lined by bland cuboidal cells. (**c**) Benign thymic parenchyma with a Hassall corpuscle is also present in the wall of the cyst. Magnification × 20 (**a**), × 200 (**b**, **c**)

[96]. Multilocular cysts are acquired cystic ductular dilatations due to inflammatory reaction of the thymic parenchyma and are frequently lined by squamous epithelium, but cuboidal or ciliated columnar linings are also described [97, 98]. Cholesterol granulomas and chronic inflammatory infiltrate are commonly found in the cyst wall of multiloculated thymic cysts. The lack of heterologous elements and the presence of thymic tissue underlying the epithelium should aid in the distinction from teratoma. However, seminoma and yolk sac tumors should be carefully excluded because these tumors can show similar cystic changes in the thymus as seen in a multiloculated thymic cyst [50]. Awareness of this secondary thymic change and thorough sampling are critical in excluding an associated GCT.

8.8.3 Enteric Cysts

Enteric cysts are usually found in children and adolescents and are almost exclusively located in the posterior mediastinum (paraesophageal and gastroesophageal) [99–101]. The cyst wall contains a double layer of smooth muscle and can be lined by simple or pseudostratified columnar, squamous, or gastric mucosa.

8.8.4 Bronchogenic Cysts

Bronchogenic cysts, congenital anomalies of foregut origin, can be found in any mediastinal compartment and in any age group [101, 102]. They may closely mimic mature teratomas because they are comprised of respiratory

epithelium, smooth muscle, and mature cartilage or mucous glands. Cysts with well or moderate architectural differentiation toward normal tracheobronchial structures, presence of respiratory-type epithelium, lack of enteric-type epithelium, immature elements, atypia, and tumor necrosis favor bronchogenic cyst [103]. The presence of CK7 expression in the absence of staining with CDX2 further supports bronchogenic cyst. In contrast, teratomas have a mixed enteric and respiratory epithelium, and the majority of the glands express CK7, CK20, CDX2, and TTF-1. Moreover, coexpression of CDX2 and TTF-1 was only found in teratoma [103].

8.8.5 Meningocele

Meningoceles are posterior mediastinal cysts which communicate with meninges. In general they occur in infants and children [104]. The clinical/radiographic features are usually characteristic. Microscopically, they might show various amounts of neural tissue and calcification and should not be confused with teratoma.

8.8.6 Pleuropulmonary Blastoma

In children, pleuropulmonary blastoma (PPB) can potentially mimic a GCT because of its biphasic appearance and heterologous mesenchymal differentiation [105, 106]. It can be cystic and/or solid and has sarcomatoid characteristics. It is usually found in the lung but occasionally can be identified in the pleura. The cysts are typically lined by respiratory or cuboidal epithelium and lack the squamous, gastrointestinal, or neuroglial lining often seen in teratoma (Fig. 8.9). The primitive spindled cells of PPB often resemble embryonal rhabdomyosarcoma or fibrosarcoma, patterns which are unusual in teratoma but might be present as sarcomatoid component in other GCTs. Heterologous elements such as cartilage may rarely be seen in PPB. The cyst lining together with the absence of other organized elements helps to distinguish this rare malignant tumor from a primary intrapulmonary teratoma.

8.8.7 Sarcomatoid Carcinoma

Sarcomatoid carcinomas of the lung are a broad spectrum of poorly differentiated non-small cell carcinomas that contain a sarcoma or sarcoma-like component (Fig. 8.10) [107]. The closest mimics of immature teratoma include pleomorphic carcinoma, carcinosarcoma, and pulmonary blastoma. Pleomorphic carcinoma contains a component of morphologically typical non-small cell carcinoma (i.e., squamous cell carcinoma, adenocarcinoma, or large cell carcinoma) admixed with a malignant spindle cell component lacking a specific line of heterologous differentiation. The obvious non-small cell lung carcinoma component should allow distinction from immature teratoma or PMGCT with sarcomatoid component in most cases. Carcinosarcoma, like pleomorphic sarcoma, is comprised of non-small cell carcinoma, but, in contrast to pleomorphic sarcoma, also contains a differentiated sarcomatous component (e.g., chondrosarcoma, rhabdomyosarcoma, osteosarcoma) (Fig. 8.11) [77]. Again, the presence of typical non-small cell lung carcinoma should allow the distinction in most cases. The closest histologic mimic of teratoma is the pulmonary blastoma [108–110]. Despite the name, this is a tumor predominantly of adults characterized by an admixture of fetal-type adenocarcinoma (tubules lined by pseudostratified columnar, nonciliated epithelium with clear to lightly eosinophilic cytoplasm) and embryonic mesenchyme, both of which resemble fetal lung between 10 and 16 weeks of gestation [111]. The glands often have supranuclear or subnuclear vacuoles and sometimes show squamous morular metaplasia creating an endometrioid appearance. The condensation of the spindle cell component around the glands may closely mimic immature teratoma, especially if heterologous differentiation is present. Recognition of the typical fetal-type gland morphology is key to this distinction.

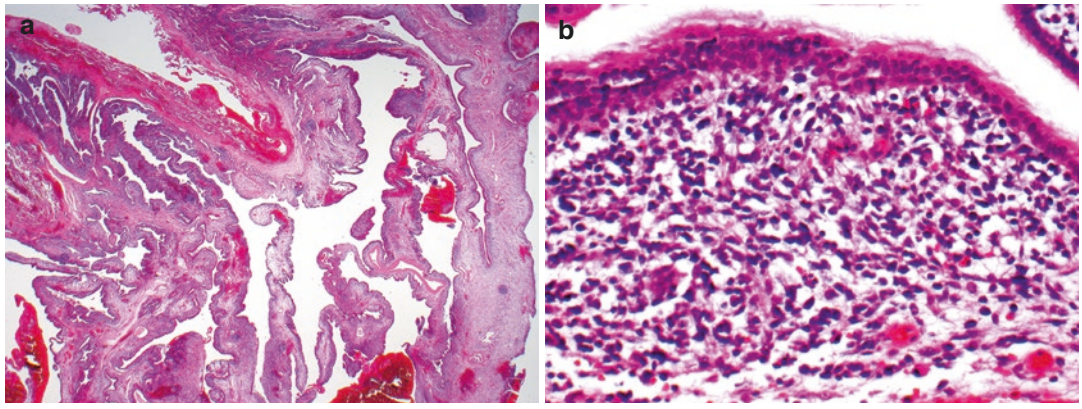

Fig. 8.9 Pleuropulmonary blastoma. (**a**) Low magnification reveals a multicystic tumor. (**b**) The cystic spaces are lined by respiratory epithelium. A population of primitive malignant small round blue cells is beneath the cyst lining. Magnification × 12.5 (**a**), 400 (**b**)

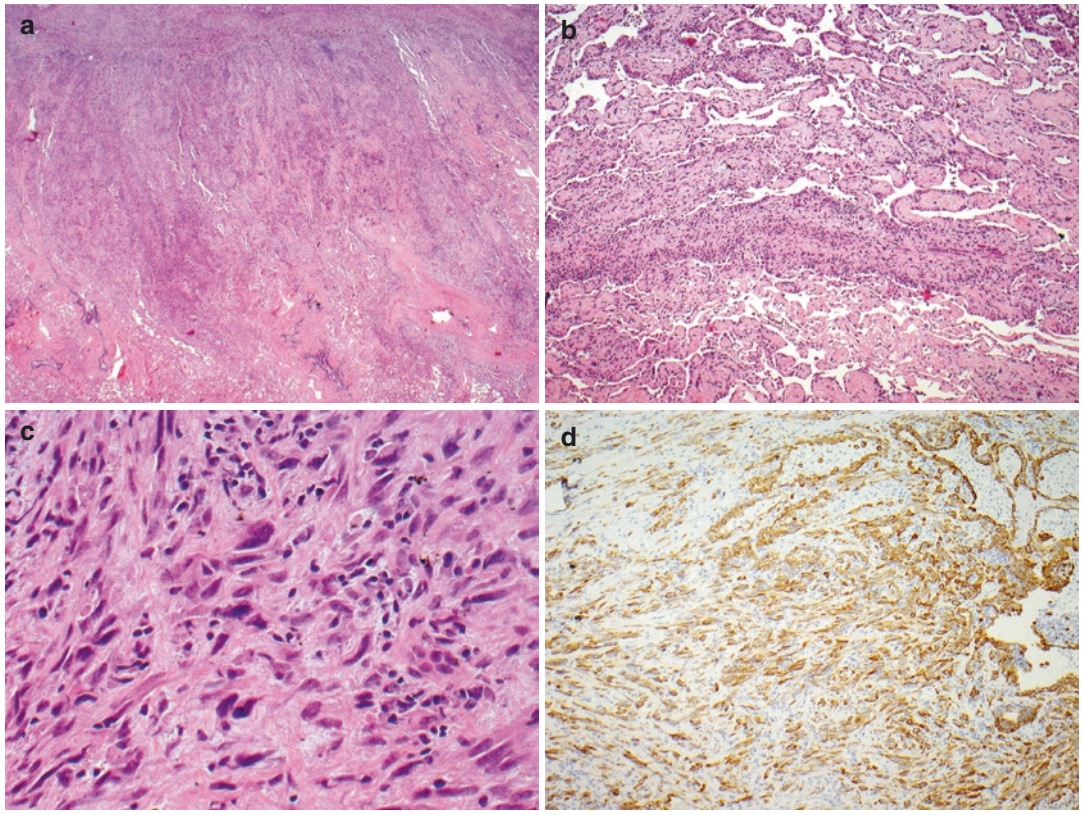

Fig. 8.10 Sarcomatoid carcinoma. (**a**) Low-power view shows a hypercellular malignancy in a fibrotic background. Malignant spindle cells are growing in sheets or along preformed structures, in this case leading to thickening of the pulmonary interalveolar septum (**b**) Neoplastic spindle cells have large nuclei with irregular borders and dark chromatin (**c**) and mark with keratin AE1/AE3 (**d**) Magnification × 20 (**a**), 100 (**b**, **d**), 400 (**c**)

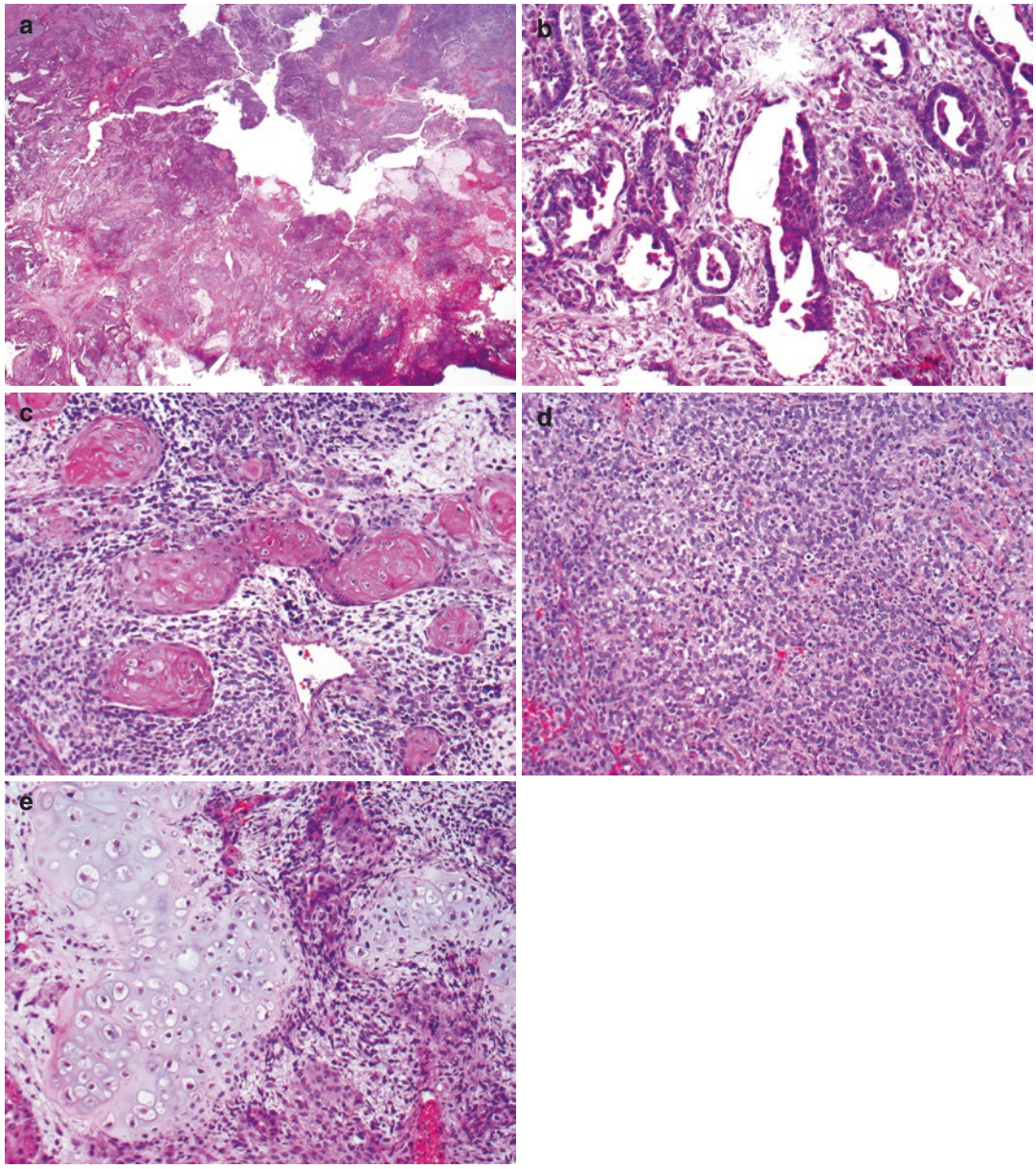

Fig. 8.11 Carcinosarcoma. (**a**) Low-power view shows a biphasic neoplasm that is comprised of an epithelial (glandular, squamous, and undifferentiated) and a mesenchymal (malignant cartilage) component. High-power microscopy reveals neoplastic glands (**b**), focal squamous differentiation (**c**), sheets of neoplastic epithelioid cells to suggest undifferentiated carcinoma (**d**), and neoplastic cartilage (**e**). Magnification × 12.5 (**a**), × 200 (**b**–**e**)

8.8.8 Non-small Cell Carcinoma

Embryonal carcinoma and, at times, seminoma can have significant morphologic overlap with a poorly differentiated carcinoma (e.g., pulmonary, thymic, or metastatic). Metastatic carcinomas with clear cytoplasm, such as clear cell renal cell carcinoma, may further mimic either yolk sac tumor or seminoma. The coexpression of cytokeratin and CD30 is characteristic of embryonal carcinoma, but not entirely specific. OCT4 appears relatively specific for seminoma and

embryonal carcinoma [79–81, 112]. Markers of other primary carcinomas such as TTF-1 (lung) and gross cystic disease fluid protein-15 (breast/salivary gland) may also be useful in this setting. Lung carcinomas can express AFP, beta-HCG, and placental lactogen [90, 113], a finding that should not be interpreted out of the morphologic and clinical context as evidence of a GCT.

Lung cancer is an important differential diagnosis of choriocarcinomas in the mediastinum as they also can produce beta-HCG. Therefore, expression of beta-HCG by the tumor cells or positive serology is not diagnostic of choriocarcinoma in the mediastinum. FISH for isochromosome 12p might be helpful since the presence of isochromosome 12p in the tumor cells is diagnostic of GCT and argues against lung cancer. However, the lack of isochromosome 12p does not exclude GCT since not all GCTs harbor isochromosome 12p.

8.8.9 Granulomatous Disease

In the mediastinum, granulomatous disease opens a rather broad differential diagnosis including infection and sarcoidosis. Non-small cell carcinoma or lymphoma can also present with a granulomatous reaction. However, the possibility of a seminoma should at least be considered [77]. In seminoma, close examination will generally reveal scattered neoplastic cells typical of seminoma. Immunostains for OCT4 can be very helpful in highlighting and confirming the diagnosis in cases with minimal disease. Rarely, GCTs other than seminoma may be associated with abundant granulomatous inflammation.

8.8.10 Lymphoma

Lymphoma is relatively common in the mediastinum [77]. Although usually seen in the younger patient, the mediastinum can be involved by lymphoma in any age group. Mediastinal (thymic) large B-cell lymphoma, diffuse large B-cell lymphoma, lymphoblastic lymphoma, anaplastic large cell lymphoma (ALCL), and classic Hodgkin lymphoma may potentially mimic embryonal carcinoma or seminoma. Immunostains for cytokeratin should highlight embryonal carcinoma, and OCT4 may be of utility as a marker of either embryonal carcinoma or seminoma in this setting. Immunostains for CD30 should not be used in isolation as a marker of embryonal carcinoma because of the shared expression in a variety of lymphomas (e.g., Hodgkin lymphoma, ALCL, mediastinal large B-cell lymphoma) [114]. Nodular sclerosing classic Hodgkin lymphoma may mimic subtle patterns of seminoma, particularly on small biopsies or when associated granulomas are present (Fig. 8.7). The syncytial variant of Hodgkin lymphoma may closely mimic an undifferentiated carcinoma such as embryonal carcinoma because of the sheetlike growth pattern. Some hematopoietic neoplasms in this differential may also have either weak or complete absence of CD45 reactivity making their consideration on morphology critical. Other markers of hematopoietic differentiation that may be useful include CD34 and TdT (lymphoblastic lymphoma), EMA and ALK-1 (ALCL), and CD15 and PAX-5 (classic Hodgkin lymphoma).

Detection of Reed-Sternberg or Hodgkin cells that express both CD15 and CD30 favors a diagnosis of Hodgkin lymphoma (Fig. 8.7). Non-Hodgkin lymphoma comprises sheets of neoplastic lymphoid cells and associated reactive lymphocytes and may mimic typical seminoma. However, neoplastic lymphoid cells usually have less distinct cell borders, and their cytoplasm is not usually abundant or optically clear as it is in seminoma. Negative immunoreactivity for germ cell markers with positive immunostaining for lymphoid markers in lymphoma will aid its distinction from seminoma.

8.8.11 Thymoma and Thymic Carcinoma

On biopsy, thymoma, most commonly WHO type B1 or B2, may mimic GCTs with a brisk

lymphocytic infiltrate, especially seminoma (Fig. 8.4) [77]. Type B3 thymomas are characterized by sheets of epithelioid cells (Fig. 8.12). Sometimes these cells can have more cytologic atypia and may mimic GCT, especially on a biopsy. In general, seminoma has a rim of clear cytoplasm and one or more prominent nucleoli, features that might help to distinguish it from type B3 thymoma. On resection, thymoma should be recognized by its lobulated growth pattern which is usually not present in GCT (Figs. 8.4 and 8.12). Furthermore, type A and AB thymomas are comprised at least focally of bland-appearing spindle cells. Immunohistochemistry might aid in the diagnosis. A study of 46 PMGCTs including teratoma, seminoma, yolk sac tumor, embryonal carcinoma, and mixed GCTs (teratoma and yolk sac tumor; teratoma, yolk sac tumor, and seminoma) and 22 thymomas (WHO types A, AB, B1, B2, and B3) showed that OCT4 expression was restricted to seminoma, embryonal carcinomas, and mixed GCT with seminomatous component. No OCT4 staining was identified in thymomas, yolk sac tumors, teratomas, and the mixed GCT without a component of seminoma [115].

Thymic carcinoma can be distinguished from seminoma by its often marked cytologic atypia (Figs. 8.13 and 8.14). Thymic carcinomas have a wide morphologic spectrum and may show a specific line of epithelial differentiation (most commonly squamous differentiation, Figs. 8.13 and 8.14). Only rare thymic

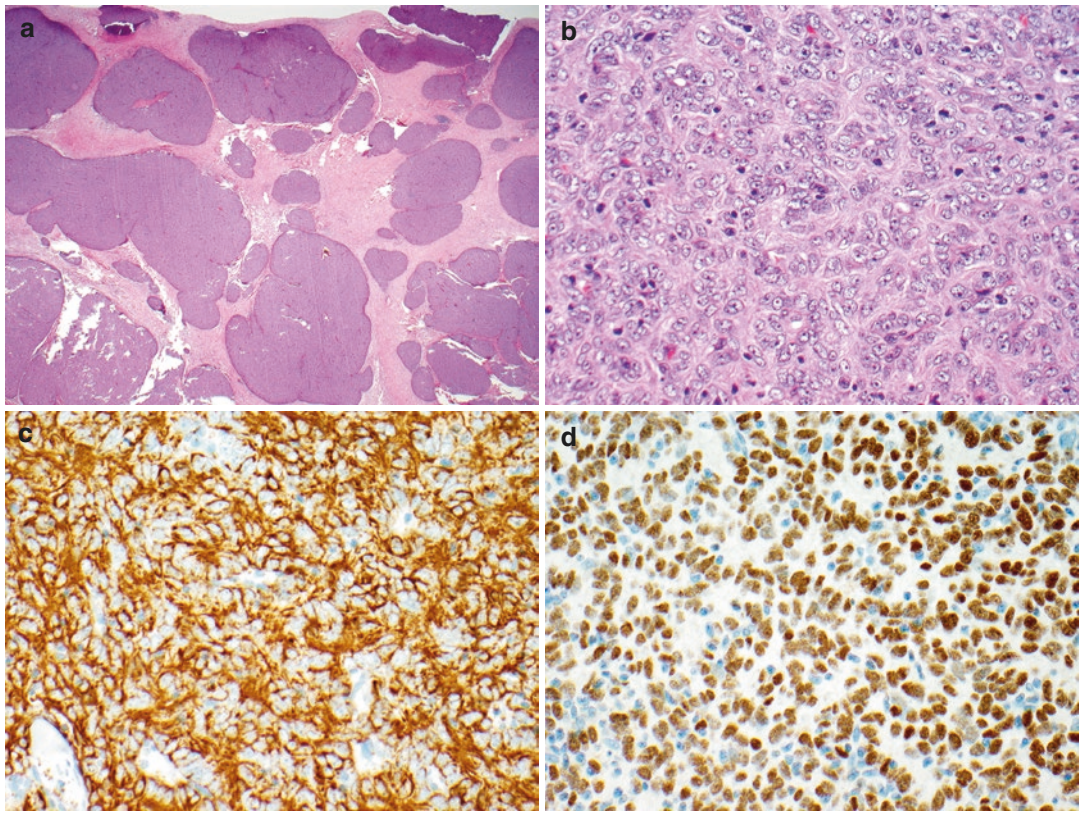

Fig. 8.12 Thymoma, WHO type B3. (**a**) On low power, a lobulated tumor contains cellular lobules that are separated by fibrous bands. (**b**) The lobules are comprised of large polygonal tumor cells that are characterized by open nuclear chromatin and prominent nucleoli. Only occasional small lymphocytes are scattered throughout the tumor. The neoplastic cells are positive for CK5/6 (**c**) and p40 (**d**). Magnification × 12.5 (**a**), × 400 (**b**–**d**)

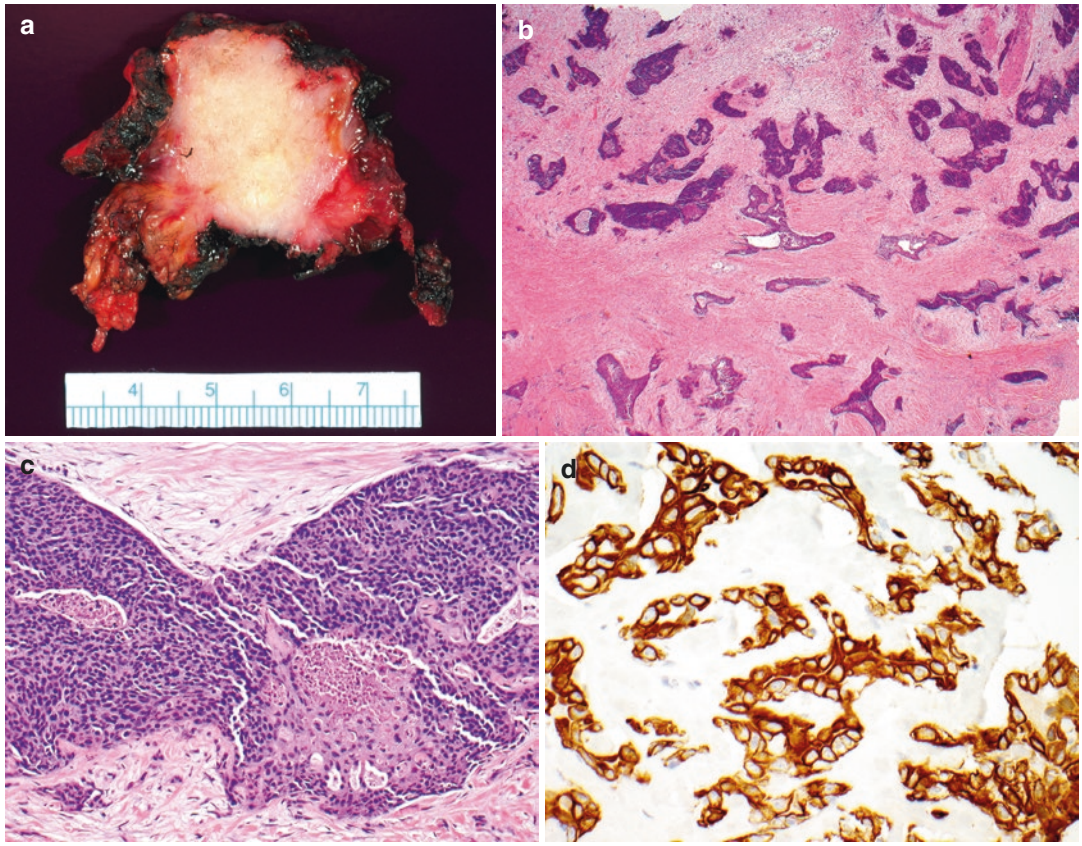

Fig. 8.13 Thymic carcinoma, squamous cell carcinoma. (**a**) The cut surface reveals a spiculated white-tan mass. (**b**) On low-power microscopy, irregular tumor cell nests are growing in a fibrotic background. (**c**) Although most tumor cells appear rather small with a high nuclear-to-cytoplasmic ratio consistent with a high-grade tumor morphology, some tumor cells are characterized by ample eosinophilic cytoplasm suggestive of squamoid differentiation. Necrosis is present. A desmoplastic stromal reaction is apparent around the tumor cell nests. The neoplastic cells are positive for CK5/6 further supporting squamous differentiation. Magnification × 20 (**b**), × 200 (**c**), × 400 (**d**)

carcinomas have prominent clear cytoplasm which may further mimic seminoma or yolk sac tumors [116]. Thymic sarcomatoid carcinomas may closely mimic immature teratoma, particularly those with heterologous differentiation. The malignant epithelial component of thymic sarcomatoid carcinoma should allow distinction from teratoma in most cases. Again, OCT4 immunostain can be helpful to distinguish thymic carcinoma from seminoma and embryonal carcinoma. CD117, however, also stains many thymic carcinomas and therefore is not useful in its distinction from seminomas (Fig. 8.14e).

8.8.12 NUT Carcinoma

Nuclear protein in testis (NUT) carcinomas are rare, aggressive carcinomas that are most commonly located in the mediastinum but also other midline organs and regions. These tumors have a characteristic t(15;19). Patients are usually young with a median age of 16 years; however, more recently this tumor was also identified in older patients. The reported age ranges between 0.1 and 78 years [117–122]. Morphologically, NUT carcinomas may mimic embryonal carcinoma with a lymphoepithelioma-like appear-

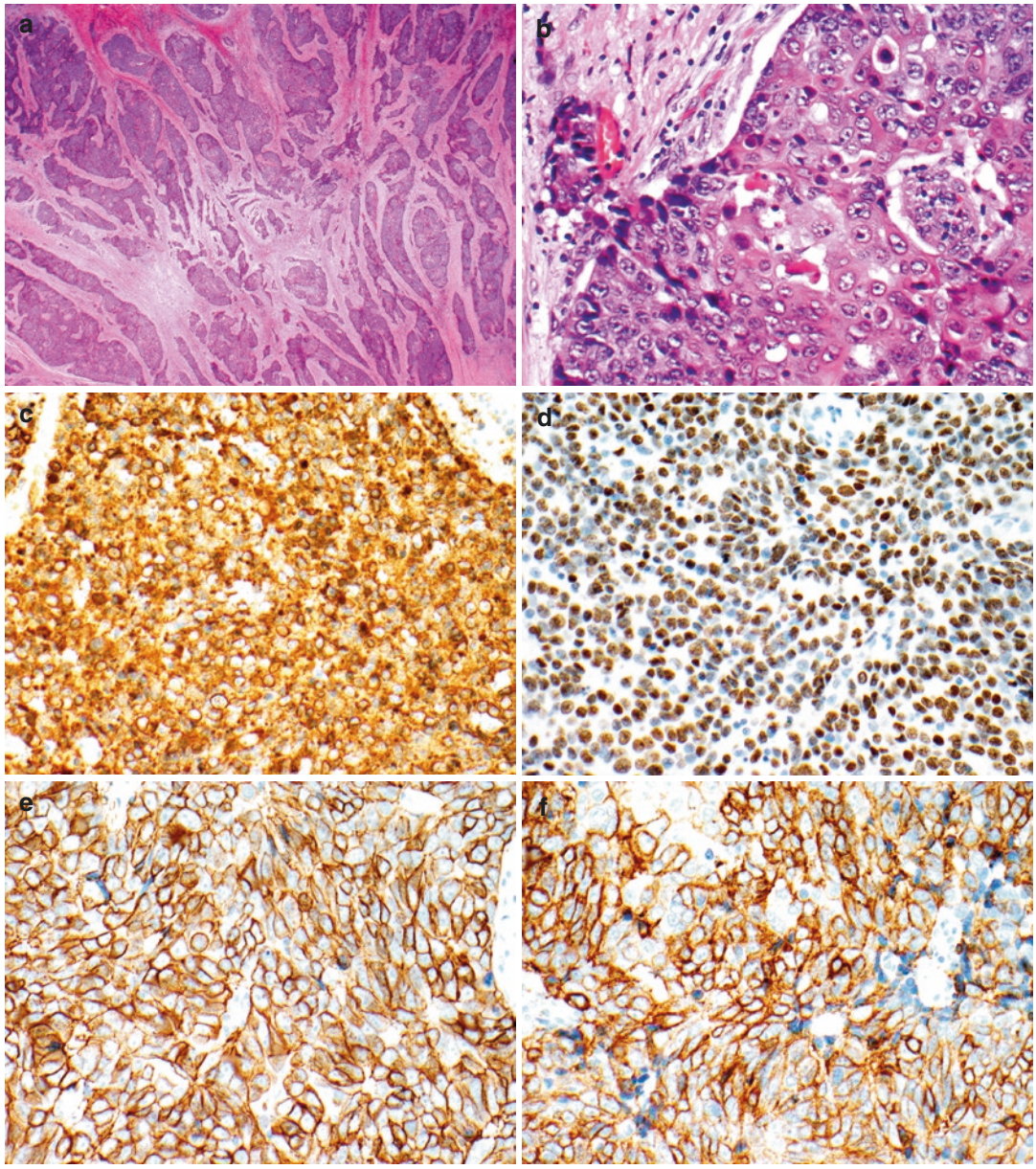

Fig. 8.14 Thymic carcinoma, squamous cell carcinoma. (**a**) This thymic carcinoma is more cellular but also characterized by cell nests growing in a fibrotic background. (**b**) On high power, the neoplastic cells are very atypical but have eosinophilic cytoplasm, and dyskeratotic features are apparent. Squamous differentiation is supported by expression of CK5/6 (**c**) and p40 (**d**) by the neoplastic cells. This thymic carcinoma also expresses CD117 (**e**) and CD5 (**f**). Magnification × 12.5 (**a**), × 400 (**b**–**f**)

ance. Although may be difficult in biopsies, the presence of squamous differentiation in the NUT carcinoma should help in the distinction from embryonal carcinoma, and diagnoses may be confirmed by NUT immunostain, FISH, or RT-PCR (Fig. 8.15) [123].

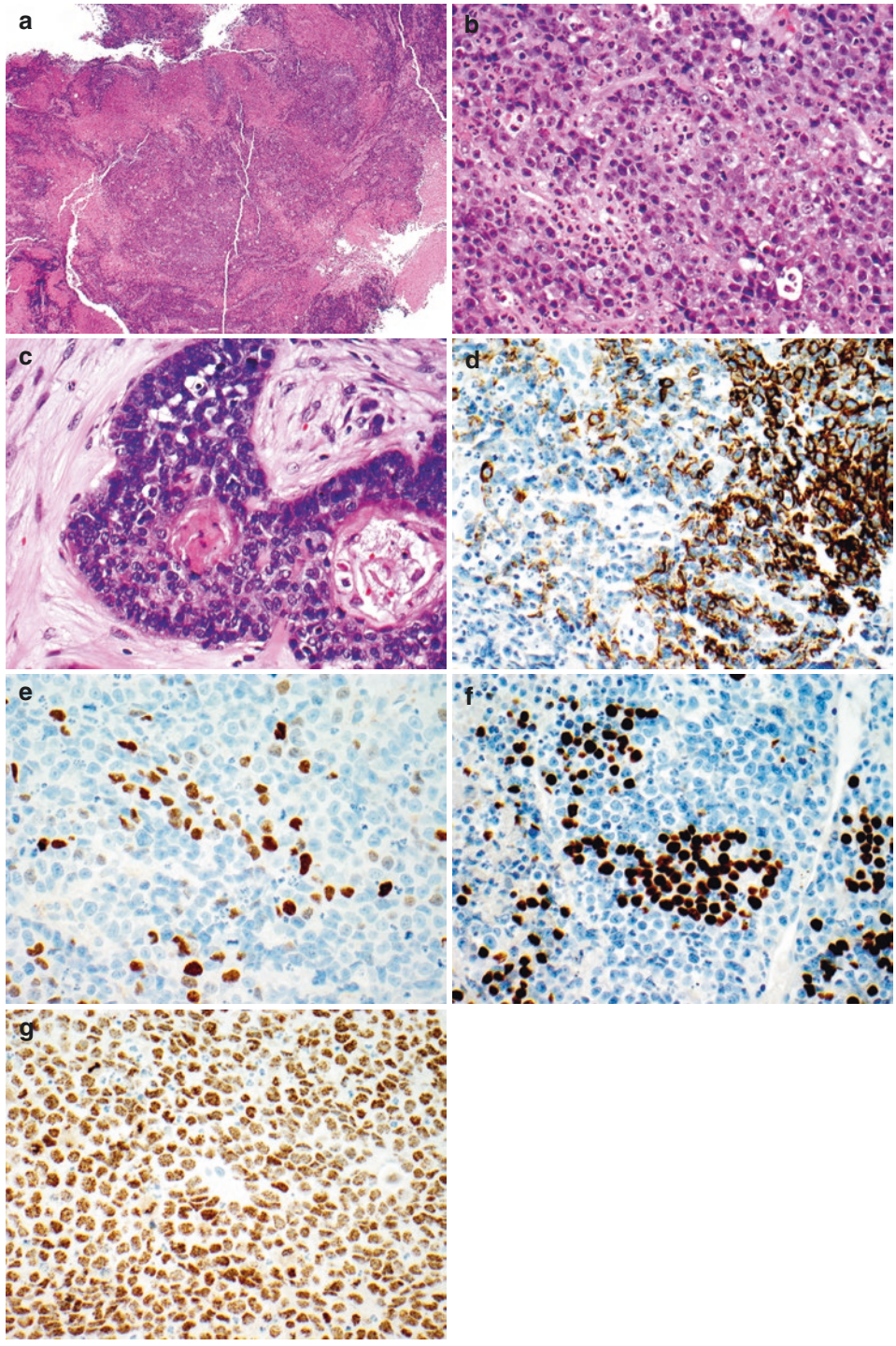

Fig. 8.15 NUT carcinoma. (**a**) On low power, sheets of neoplastic cells are intimately associated with large areas of necrosis. (**b**) The neoplastic cells are of epithelioid, relatively monomorphous cytology with round to oval nuclei, open nuclear chromatin and prominent nucleoli. (**c**) Abrupt keratinization is apparent. The majority of the neoplastic cells is positive for OSCAR keratin (**d**), and subsets of neoplastic cells express p40 (**e**) and/or TTF-1 (**f**). The neoplastic cells are diffusely positive for NUT exhibiting a characteristic speckled staining pattern (**g**). Magnification × 40 (**a**), × 400 (**b**–**g**)

8.8.13 Epithelioid Angiosarcoma

Angiosarcomas, when epithelioid in phenotype, may mimic embryonal carcinoma [124]. The identification of vascular lumen formation, the expression of vascular markers (CD31, CD34, Fli-1), and the absence of OCT4 reactivity should allow the distinction in most cases. Care should be taken in the interpretation of CD31 as intratumoral macrophages, which are typically present after adjuvant therapy, can show strong cytoplasmic reactivity [125].

8.8.14 Synovial Sarcoma

This biphasic sarcoma may occur as a primary mediastinal tumor [126] and could mimic immature teratoma. The spindle cell component of synovial sarcomas has a very distinct appearance with a monomorphic population of spindled cells arranged in tight intersecting fascicles. The glandular component may be focal, but it typically does not demonstrate any obvious mucinous or squamous differentiation as is often seen in teratoma. TLE-1 immunostain and/or molecular confirmation of the synovial sarcoma specific t(X;18) may be helpful.

8.8.15 Malignant Mesothelioma

Malignant mesothelioma has a broad morphologic spectrum that may overlap with several different GCTs, particularly given the shared expression of cytokeratin. Epithelioid mesothelioma can mimic a variety of carcinomas depending on the pattern present (Fig. 8.16). The tubulopapillary and microcystic (adenomatoid) epithelioid patterns may resemble yolk sac tumor, whereas poorly differentiated epithelioid mesothelioma can mimic embryonal carcinoma. Rare mesotheliomas have a myxoid morphology with clusters and cords of epithelioid cells set in pools of myxoid material, a pattern that may appear similar to the myxoid pattern of yolk sac tumor [127]. Biphasic mesothelioma could potentially mimic an immature teratoma if the epithelial component has somewhat bland cytologic features. Heterologous bone and cartilage differentiation has been documented in sarcomatoid mesotheliomas, a feature that could be mixed up with teratoma [128]. Sarcomatoid mesothelioma might mimic sarcomatous heterologous differentiation of immature teratoma. However, immunostains including OCT4 and conventional mesothelial markers together with the clinical setting such as a diffuse growth of the tumor along serosal surfaces should allow distinction from a GCT in most cases.

8.8.16 Congenital Peribronchial Myofibroblastic Tumor

Congenital peribronchial myofibroblastic tumor is a proliferation of cytologically bland myofibroblasts in the lung of newborns that can potentially mimic teratoma when bronchial epithelium and cartilage become entrapped [129]. This proliferation can efface the lung parenchyma, but often involves the interstitium and peribronchovascular areas. Recognition of the interstitial distribution and the entrapped nature of the epithelial and cartilaginous components should allow distinction from teratoma.

8.8.17 Pulmonary Hamartoma

Pulmonary hamartoma is a benign lung neoplasm that is composed of different mesenchymal tissues with entrapped respiratory-type epithelium (Fig. 8.17). The mesenchymal component is typically mature hyaline cartilage, but bone, fat, and smooth muscle may also be present. The tumor is recognized by invagination of respiratory epithelium into the tumor.

8.8.18 Metastatic Melanoma

Metastatic melanoma can mimic any poorly differentiated malignant neoplasm, including embryonal carcinoma. Recognition of the subtle nesting of the neoplastic cells and verification of

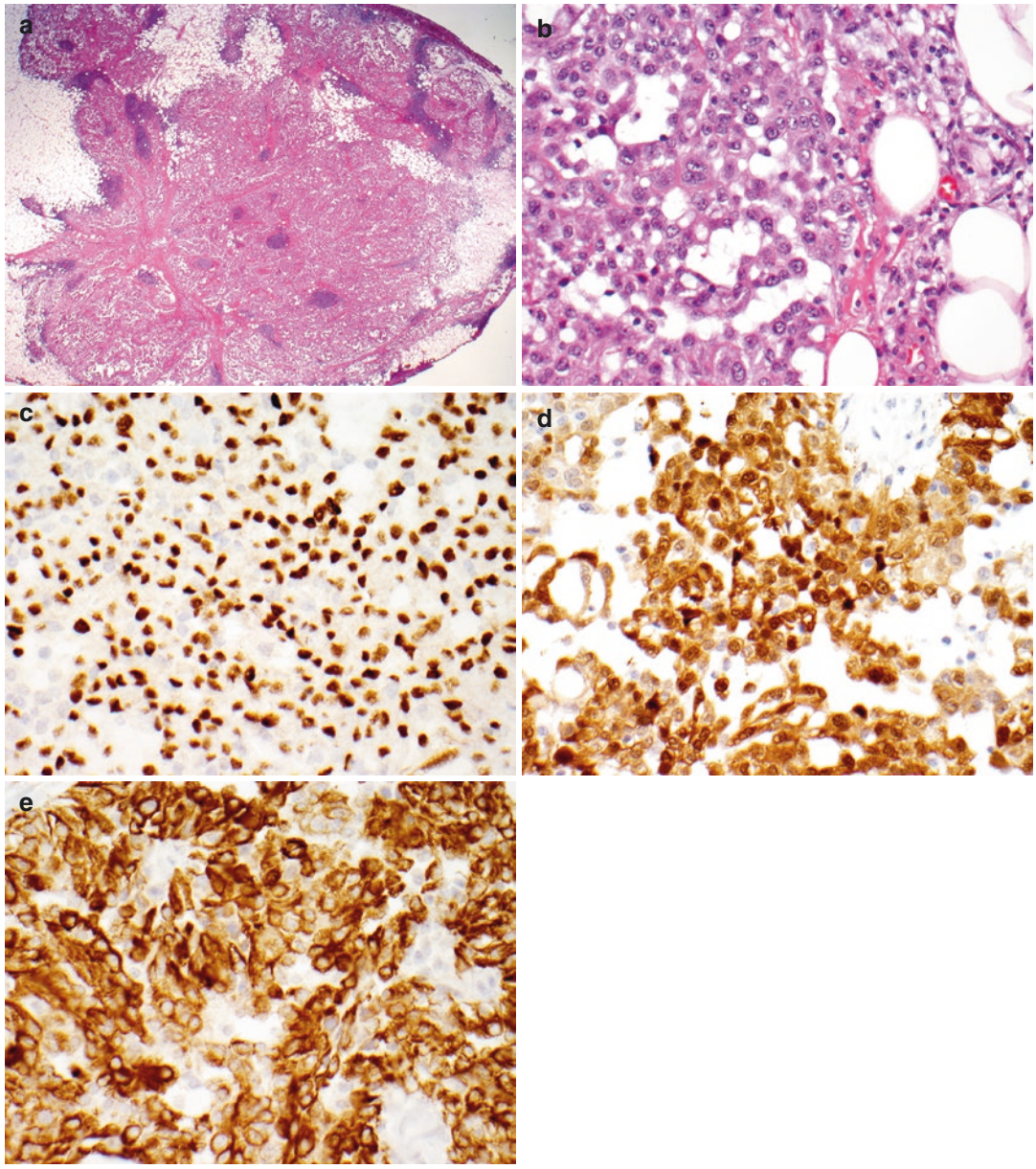

Fig. 8.16 Malignant mesothelioma, epithelioid type. (**a**) Sheets of neoplastic cells are growing in an infiltrative pattern invading into adipose tissue. (**b**) The neoplastic cells are round to oval and are characterized by a fair amount of cytoplasm and round nuclei with open chromatin and conspicuous nucleoli. The neoplastic cells are positive for mesothelial markers including WT-1 (**c**), calretinin (**d**), and CK5/6 (**e**) and lack staining with carcinoma markers such as pCEA, MOC-31, and TTF-1 (not shown). Magnification × 12.5 (**a**), 400 (**b**–**e**)

melanocytic markers in the absence of OCT4 expression should resolve most cases. The absence of a history of a cutaneous melanoma should not preclude this diagnosis because in some cases a primary lesion cannot be identified, possibly secondary to regression.

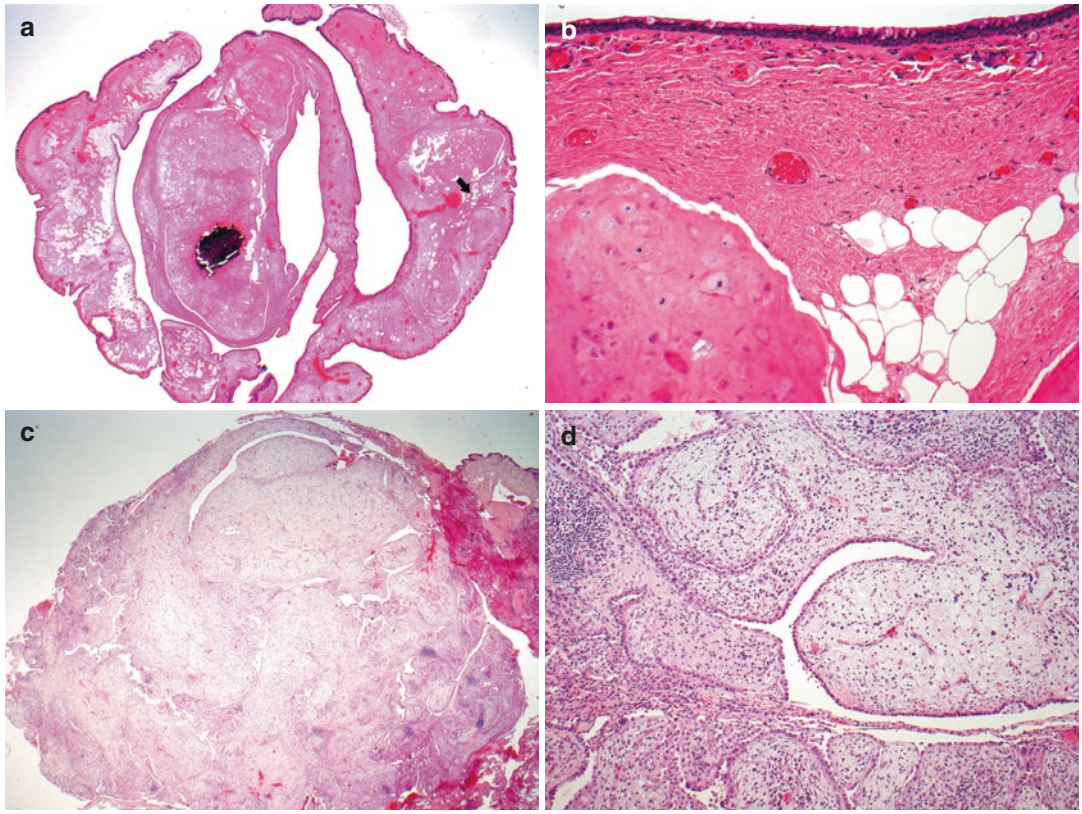

Fig. 8.17 Pulmonary hamartoma: (**a**) A well-circumscribed nodule is predominantly comprised of hyaline cartilage with focal calcification. Adipose tissue is also present (*arrow*). (**b**) Respiratory epithelium invaginates into the nodule. (**c**) This hamartoma is predominantly comprised of bland fibrovascular stroma with focal adipose tissue. (**d**) Bland cuboidal epithelial cells invaginate into the nodule. Magnifications × 12.5 (**a**), 200 (**b**), 40 (**c**), 100 (**d**)

8.9 Staging of Mediastinal Germ Cell Tumors

Clinical and pathologic staging is very important in the prognosis of PMGCTs. Unfortunately, there is not an officially recognized UICC-TNM staging protocol for PMGCTs. The WHO recommends using a modification of the AJCC TNM staging of soft tissue tumors [67].

In 1997, Moran and Suster [68] examined 322 cases of PMGCT and proposed a staging system specifically for these tumors based on the clinical outcome of their cases (see Table 8.6). The author's recommendation was to treat tumors that are confined to the mediastinum without infiltration of adjacent structures (stage I) conservatively, with surgery alone or with surgery, and an added modality based on the histology of the tumor. Lesions of advanced stage (II or III) would require more aggressive treatment with curative intent, whereas palliative treatment was the choice in tumors with extrathoracic metastasis. This staging approach correlated well with the clinical outcome of the patients in that study.

Staging of pediatric extragonadal GCT is summarized in Table 8.7.

8.10 Outcome of Mediastinal Germ Cell Tumors

The 5-year relative survival of patients with mediastinal GCTs is 58 % according to SEER registries [13]. The prognosis depends on the histologic

Table 8.6 Clinical staging of mediastinal germ cell tumors as proposed by Moran and Suster

Stage I	Well-circumscribed tumor with or without focal adhesions to the pleura or pericardium but without microscopic evidence of invasion into adjacent structures
Stage II	Tumor confined to the mediastinum with macroscopic and/or microscopic evidence of infiltration into adjacent structures (i.e., pleura pericardium and great vessels)
Stage III A B	Tumor with metastases Metastases to intrathoracic organs (lymph nodes, lung, etc.) Extrathoracic metastases

From Moran et al. [68], with permission

Table 8.7 Staging of pediatric extragonadal extracranial GCT as defined by the Children's Oncology Group (COG) [189]

Stage	Characteristic
I	Localized disease; complete resection with no microscopic disease at margins or in regional lymph nodes. Tumor markers must normalize in appropriate half-life after resection. Complete coccygectomy for sacrococcygeal site
II	Microscopic residual disease, capsular invasion, and/or microscopic lymph node involvement. Tumor markers fail to normalize or increase
III	Gross residual disease and gross lymph node involvement (>2 cm)
IV	Distant metastases, including the liver, brain, bone, or lung

subtype with pure mediastinal seminomas having a much better outcome than tumors with a non-seminomatous component.

Mediastinal seminomas respond favorably to radiation therapy and/or cisplatin-based chemotherapy [130]. For instance, patients with mediastinal seminomas treated with cisplatin-based combination chemotherapy have a 5-year survival of 90–100 % and an overall survival of 88–90 % [41, 130–132]. In mediastinal seminomas, factors that have been suggested to be associated with greater rate of progression include patient's age over 35 years, presentation with fever, SVC syndrome, supraclavicular or cervical adenopathy, and radiologic evidence of hilar disease [30]. The most important feature to predict outcome is whether the patient has disease limited to the mediastinum or has widespread disease to adjacent organs of the thoracic cavity or outside of the thorax. Metastasis to the liver or other non-pulmonary visceral metastases and metastases to two or more sites are poor prognostic factors [130]. Recurrences have been reported after many years of remission [133]. A correlation between aggressive behavior and any clinical or histopathologic features has not been identified in mediastinal seminomas [51].

The outcome for primary mediastinal immature teratoma and nonteratomatous GCTs is worse than for their gonadal counterpart. Mediastinal non-seminomatous GCT have only a 40–50 % overall survival after platinum-based chemotherapy and surgery [134–136] and a 5-year survival rate of 48 %, according to the International Germ Cell Cancer Collaborative Group consensus classification [134].

If there is metastatic disease to the lung, liver, or supraclavicular lymph nodes, the overall survival drops to 25 %. Patients who relapse after initial cisplatin-based chemotherapy have an extreme dismal outcome with an overall survival of only 10 %. Surgical resection of residual disease after chemotherapy shows residual viable tumor in 30–47 % of patients [137, 138]. Factors that contribute to inferior survival include an overall poorer response to chemotherapy and higher incidence of degenerative non-germ cell cancer pathology in the residual mass [139]. Age ≥12 years is also suggested as an adverse prognostic factor [77].

Outcomes of these patients are improving with preoperative cisplatin-based combination chemotherapy strategies [130–132, 140]. With neoadjuvant chemotherapy, good prognostic factors include completeness of resection, less than 10 % viable tumor cells, and low-risk group as defined by the International Germ Cell Consensus Classification Group [134].

Primary mediastinal choriocarcinomas have a much worse prognosis than other histologic subtypes because of hematogenous dissemination at the time of diagnosis [141]. However, under current chemotherapeutic regimens, the prognosis of choriocarcinomas has improved [69].

Embryonal carcinomas and yolk sac tumors, whether pure or in association with any other components (seminoma or teratoma), have a similar outcome and are generally regarded as poor prognostic findings.

As in congenital teratomas, the prognosis of PMGCTs in children is significantly affected by tumor stage and completeness of surgical excision [142].

Epidemiologic studies have shown that patients with PMGCTs have an increased risk for death related to hematopoietic malignancies and cardiovascular disorders, but no significant difference in risk of dying from solid cancers compared to patients with gonadal GCTs was identified [12]. In fact 6 % of primary mediastinal non-seminomatous GCT develop hematologic malignancies, the most common being acute megakaryoblastic leukemia (AML-M7) and myeloblastic syndromes [143]. These hematopoietic tumors may involve the PMGCT or be completely extramediastinal. A pathogenetic hypothesis is that hematopoietic stem cells arise in the yolk sac [144]. Another hypothesis is that a teratoma containing all three germ layers with varying degrees of differentiation undergoes malignant transformation to leukemia in the bone marrow. Interestingly, cytogenetic analysis of bone marrow aspirates reveals i(12p) in 38 % of patients [145], a cytogenetic abnormality that is commonly seen in PMGCT, indicating a possible common biologic pathway. GCT-associated acute leukemias are an ominous finding as they are typically refractory to current treatment modalities with a reported survival of less than 2 years in all reported patients. The main differential diagnostic consideration in this setting is a therapy-related myelodysplastic syndrome or acute leukemia following etoposide administration [143]. Therapy-related diseases can be distinguished by their occurrence later in the course (25–60 months), the absence of i(12p), and the possible presence of an etoposide-related translocation such as 11q23 [146–148].

The "growing teratoma syndrome" [139] defines a mediastinal mass that is growing subsequently to neoadjuvant therapy and is associated with secondary cardiopulmonary deterioration precluding safe completion of planned chemotherapy in the presence of declining serum tumor markers. The term was first coined by Logothetis and colleagues [149] who reported patients with non-seminomatous testicular cancer and growing retroperitoneal or lung masses during observation after chemotherapy. In the mediastinum, five (of 188) patients who underwent postchemotherapy surgery for primary mediastinal non-seminomatous GCT were identified [139]. These five men had an average age of 25.8 years (range, 20–33 years). All patients presented at the time of diagnosis with a large symptomatic anterior mediastinal mass and elevated AFP at an average of 9137 ng/mL (range, 791–36,000 ng/mL). HCG was elevated in three patients with a mean of 206 mIU/mL (range, 8–350 mIU/mL). CT revealed evidence of metastatic disease (lung) in one patient at the time of diagnosis, with the remaining patients presenting with disease isolated to the mediastinum. Prechemotherapy biopsies demonstrated mature teratoma in only two patients despite elevated AFP, mature teratoma and foci of non-seminomatous germ cell tumor in two patients and one patient with immature teratoma and foci of non-seminomatous GCT. Three patients had normalized serum tumor markers, and two patients demonstrated rapid serum tumor marker decline before surgery. All five patients underwent complete surgical resection of the mediastinal mass with tumor-free margins. The two patients who had not normalized but demonstrated rapid serum tumor marker decline at the time of surgery had normalized tumor markers by the time of hospital discharge. Surgical pathology of the mediastinal mass demonstrated mature teratoma only and mature teratoma with focal immaturity in one patient each. Pathology was mixed in the other three patients with predominately mature teratoma and focal yolk sac tumor ($n = 1$), non-GCT (angiosarcoma, $n = 1$), and a combination of yolk sac and non-GCT (angiosarcoma, $n = 1$). One patient died of respiratory failure postoperatively. Three of the 4 surviving patients received cisplatin-based chemotherapy after recovery to complete four cycles. Two patients

are alive and well 13 and 15 years after initial surgery; however, both have required further resection of metastases during follow-up. The other two patients died of metastatic non-GCT after 20 and 26 months.

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